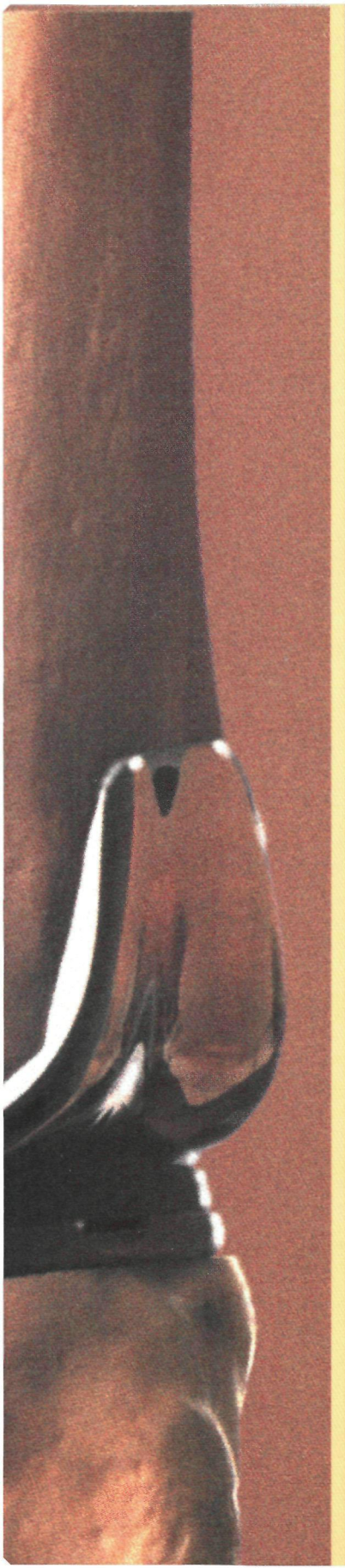

Joint sepsis after prophylaxis with one or three doses of cefuroxime in hip and knee replacement surgery

A randomized controlled multicentre trial with 3013 operations

Ate B. Wymenga

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Een wetenschappelijke proeve op het gebied van de geneeskunde en tandheelkunde

Proefschrift ter verkrijging van de graad van doctor aan de Katholieke Universiteit te Nijmegen volgens het besluit van het college van decanen in het openbaar te verdedigen op vrijdag 3 mei 1991 des namiddags 3.30 precies.

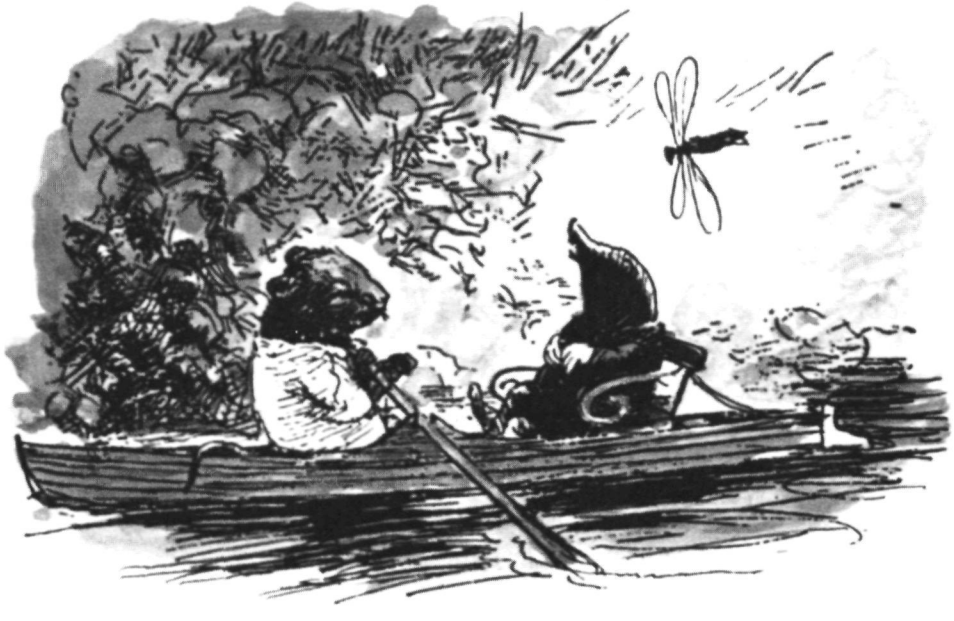
Door Ate Binne Wymenga geboren op 6 februari 1957 te Oudega (Smallingerland)

Promotor:
Prof. dr. T.J.J.H. Slooff

Co-promotores:
Dr. J.R. van Horn
Dr. H.L. Muytjens
Dr. O.M. Lidwell (Medical Research Council, Common Cold Unit, Harvard Hospital, Salisbury, Wiltshire, U.K.)

"Believe me, my young friend", said the Water Rat to the Mole, "there is nothing - absolutely nothing - half so much worth doing as simply messing about in boats. Simply messing about in boats or with boats. In or out of 'em, nothing seems really to matter, that's the charm of it. Whether you get away, or whether you don't; whether you arrive at your destination or whether you reach somewhere else, or whether you never get anywhere at all, you're always busy, and you never do anything in particular; and when you've done it there's always something else to do, and you can do it if you like but you'd much better not."

(From: *The Wind in the Willows* by Kenneth Grahame, Methuen Children's Books Ltd, Great Britain, originally published 8 October 1908)



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This study was initiated at the Orthopaedic Institute of the St.Radboud Hospital, University of Nijmegen by the late prof. dr. Th.J.G. van Rens in 1986 and prof. dr. G. v/d Ploeg. After the death of prof. van Rens, the study was continued under the supervision of prof. dr. T.J.J.H. Slooff and dr. J.R. van Horn, who actively supported the project with their expertise and inspiring enthousiasm.
Drs. A. Theeuwes (Department of Statistics) supported the study group from the very first. He carefully monitored the methodology during the performance of the trial and his nuanced statistical calculations made a clear analysis possible.
Dr. H.L. Muytjens (Department of Medical Microbiology) showed never ending dedication to the project in the bacteriological as well as in other fields. His work played an important role in the completion of the study.
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The Orthopaedic Departments from the following hospitals participated: St. Radboud Hospital - Nijmegen, St. Andreas Hospital - Amsterdam, St. Josef Hospital - Eindhoven, Leyenburg Hospital - Den Haag, St. Antonius Hospital - Nieuwegein, St. Jans Gasthuis - Weert, St. Geertruiden & St. Josef Hospital - Deventer, Rijnstate Hospital - Arnhem, Wezenlanden Hospital - Zwolle, R.K.Ziekenverpleging - Hilversum, Diaconessen Hospital - Eindhoven, Oudenrijn Hospital - Utrecht, Rode Kruis Hospital - Den Haag, Bleuland Hospital - Gouda, Catharina Hospital - Eindhoven, Laurentius Hospital - Roermond, Juliana Hospital - Apeldoorn, Juliana Hospital - Hengelo, Eudokia Hospital - Rotterdam, Diaconessen Hospital - Meppel, Bronovo Hospital - Den Haag, Bethesda Hospital - Hoogeveen, Lukas Hospital - Apeldoorn, Waterland Hospital - Purmerend, St. Josef Hospital - Oosterhout, Bergweg Hospital - Rotterdam.

I was delighted with the high quality of the trial data and the encouraging interest and enthousiasm for the study I encountered during the frequent visits to these hospitals, which made it easy to continue the study.

Contents

Chapter I
Introduction

Joint replacement surgery has become the most widely accepted operation to treat a variety of disabling pathological conditions of the hip and, to a lesser extend, also of the knee joint. The procedure has now come closer to an industrial process than any other surgical form of surgery and in the Netherlands this operation is estimated to be performed more than 10.000 times annually[1,2]*.
The incidence of joint sepsis after hip replacement has decreased from 10 percent in the late 1960s to around one percent nowadays[1] and 2-3 % after knee replacement[3]. However, the consequences of joint sepsis after prosthesis implantation are still devastating. The prosthesis often has to be removed and for many patients the final result is resection arthroplasty or arthrodesis or even amputation. The functional outcome is nearly always much poorer than anticipated before the operation and many patients suffer from pain with these conditions. Reimplantation is only performed in a limited number of patients under favourable conditions[4].

The majority of the infections are initiated during operation, and prospective randomized trials have documented the value of perioperative antibiotics[5-7]. Lidwell et al.[7] have clearly established that clean air systems are effective in reducing the incidence of joint sepsis. The current literature on the etiology, prophylaxis and diagnosis of prosthesis related infections are summarized in chapter II.

Most Dutch hospitals do not have clean-air facilities in their operating theatres. Therefore, systemic antibiotics are used routinely in joint replacement surgery. A one day (24 hour) antibiotic regimen is well-accepted[8]. In other surgical fields, a single perioperative dose of antibiotics is becoming an increasingly popular means of infection prophylax-

* These figures refer to the references at the end of each chapter

is[9] and this trend is also being adopted in orthopaedic joint replacement surgery.

As the efficacy of a single perioperative antibiotic dose has not been investigated in joint replacement surgery, we decided to start a prospective randomized controlled trial on this subject. Statistical calculations showed that a large study population was needed, comprising a group of approximately 1250 patients who would receive a single dose and a control group of 1250 patients who would receive three doses of an antibiotic (type I error 5% and type II error less than 20%, one-tail test)[10]. Cefuroxime was chosen as the prophylactic agent.
Orthopaedic departments situated in the central provinces of the Netherlands were invited to participate in the study and 27 contributed to the trial which took place in the period from 1 July 1986 to 1 July 1988. The follow-up was completed on 1 July 1989. The majority of the record forms were checked against the patient forms by the author, who visited the participating hospitals every two to three months.

The most important results of the dose-defining study for hip and knee replacements are reported in Chapters III and VI. A separate analysis on hip and knee patients was performed because patient characteristics and incidence of joint sepsis differed considerably.
As detailed preoperative, perioperative and postoperative data were documented prospectively for each patient, we were also able to perform an adequate risk factor analysis which enables the orthopaedic surgeon to identify patients who carry a high risk for joint sepsis. Chapters V and VI report on this subject.
Further analysis of the relation of wound and urine cultures and later joint sepsis after joint replacement is reported in Chapter VII. The additional usage of antibiotics after single and three dose cefuroxime prophylaxis is described in Chapter VIII.

It was not possible to present all simple data gathered in this study in the various chapters. Therefore, supplements with a general summary of all the used data from the dose defining study, the risk factor analysis and details on the 26 patients with joint sepsis, have been added.

References

1. Anonymus. Arthroplasty infections. Antisepsis and asepsis in orthopaedics. *Acta Orthop. Scand. 58* 1-3, 1987.
2. Rens Th J.G. van, Totale heup prothese, indicaties, resultaten, levensduur. *Ned. Tydschr. voor Geneesk. 130, 40:* 1782-1787, 1986.
3. Knutsson K., Lindstrand A., Lidgren L., Survival of knee arthroplasties. *J. Bone and Joint Surg. 68B·* 795-803, 1986.

4 Rand J A , Morrey B F , Bryan R S , Management of infected total joint arthroplasty *Orthop Clin N Am 15* 491-504, 1984
5 Ericson C , Lidgren L , Cloxacillin in the prophylaxis of postoperative infections in the hip *J Bone Joint Surg 55A* 808-813, 1973
6 Hill C , Mazas F , Flamant R , Evrard J , Prophylactic cefazolin versus placebo in total hip replacement *Lancet 1* 795-797, 1981
7 Lidwell O M , Elson R A , Lowbury E J L , Whyte W , Blowers R , Stanley S J , Lowe D , Ultraclean air and antibiotics for prevention of postoperative infection *Acta Orthop Scand 58* 4-13, 1987
8 Walenkamp G H I M , Antibiotica in de orthopaedie *Geneesmiddelenbulletin 20, 7,8* 35-42, 1986
9 Dipiro J ,Cheung R , Bowden T , Mansberger J A , Single-dose systemic antibiotic prophylaxis of surgical woundinfection *Am J Surg 152* 552-559, 1986
10 Pocock S J , *Clinical Trials A Practical Approach* John Wiley & Sons, Chicester, New York, Brisbane, Toronto, Singapore, 1988

Chapter II

Prosthesis-related infection

Etiology, prophylaxis and diagnosis (a review)

A.B. Wymenga*, B.J. van Dijke**, J.R. van Horn* and T.J.J.H. Slooff*

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Summary

The recent literature on prosthesis-related infections was reviewed with respect to etiology, prophylaxis and diagnosis.

Most prosthesis-related infections are initiated during the operation by contamination with bacteria-carrying particles from the air as a result of the dispersion of skin scales from individuals in the operating theatre. A small number of infections are caused by the haematogenous seeding of bacteria. Glycocalyx, a slime layer produced by the bacteria, plays an important role in the pathogenesis of infections, especially in the presence of biomaterial

Clean-air systems in combination with perioperative systemic antibiotics reduce prosthesis-related infections from 3 or 4 per cent to a few cases per thousand. The use of antibiotic-loaded bone cement is advised in high risk patients although further evaluation is needed.

Physical examination of the patient, laboratory tests including the E.S.R. and C-reactive protein, serial radiograms, isotope scanning techniques and joint aspiration, can all help to diagnose prosthesis-related infection. However, definitive diagnosis is only possible by culturing several samples of material obtained from the interface during revision surgery. A perioperative frozen section of interface tissue showing acute (more than 5 leucocytes per high power field, 500x) or severe chronic (more than 50 lymphocytes) inflammation is highly suggestive of sepsis.

Introduction

Deep infection is the most severe complication of joint replacement, resulting in significant morbidity and considerable financial cost[43,103]. Most infected prostheses must be removed and the outcome for many

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patients is resection arthroplasty or arthrodesis after multiple operations[51,103].
The purpose of this study is to review the current literature with respect to:
1. the etiology of prosthesis-related infections,
2. the subsequent prophylactic measures and
3. the efficacy of diagnostic procedures.

The literature from 1975 to 1988 was selected using MEDLINE.

Etiology

Causative microorganisms

Almost any microorganism can give rise to a prosthesis-related infection. Gram-positive, gram-negative, aerobic and anaerobic bacteria and even yeasts have been reported as causative agents[60,115]. There is no obvious distinction between pathogens and nonpathogens in this type of infection[68]. Many of these agents are skin commensals or transient skin contaminants[66].
More than 50% of well-established prosthesis-related infections are caused by gram-positive organisms (Table I). In some series, *Staphylococcus epidermidis* outnumbered *S. aureus*, indicating that this can be an important cause of prosthesis-related infection. Enteric gram-negative bacteria are responsible for 24% and anaerobic bacteria are responsible for the remaining 21% of the infections. In this latter group, anaerobic skin commensals, such as *Propionibacterium acnes* and *Peptococcus*, are frequently isolated[60].

Table I Causative agents of endoprosthesis infection (percentages of the number of isolates are given; species in mixed infections [mean 13%] are shown separately)

Author (ref.)	S. aur. %	S. epid. %	other gram + %	gram - %	anaerob. %	other %	no. of isolates
Carlsson [18]	21	31	10	11	24	2	98
Whyte [132]	8	45	-	10	37	-	51
Lidwell [67]	36	22	5	22	12	-	74
Inman [53]	18	37	13	22	10	-	68
Buchholz [12]	40	5	3	28	22	3	695
Mean	34%	13%	4%	24%	21%	2%	986

Deep infection can be initiated during an operation by the deposition of microorganisms in the open wound. Despite aseptic surgical techniques, there are three possible remaining sources of exogenous microbial contamination: contaminated air, the patient's skin and the surgeon's hand through a punctured glove[130].

Air contamination is caused by the dispersion of fragmented desquamated skin scales from individuals in the operating theatre. These particles are small enough to pass through the interstices of conventional woven cotton suits and gowns[67]. Dispersal values from an individual in a cotton scrub-suit vary between 1000-1500 colony-forming units (c.f.u.) per minute. Wearing an additional cotton gown reduces this by only 33 per cent[129].

Thus both scrubbed and non-scrubbed operating theatre personnel contribute significantly to air contamination. The amount of air contamination caused by non-scrubbed personnel may be substantially increased by movement in the operating theatre, which increases the dispersion of skin scales[67,82]. By limiting the number of persons in the operating theatre and avoiding any unnecessary activity, it is possible to significantly reduce bacterial dispersion[65].

There is an evident relationship between the number of c.f.u./m^3 in the air and the average number of bacteria washed out of the wound before closure. More bacteria are found in the wound washout in conventional operating theatres with a high degree of air contamination than in clean air conditions, where significantly fewer bacteria are recovered from the wound[65,130]. The bacterial contamination of instruments and drapes is also substantially reduced in clean air[106].

Whyte et al. (1982) concluded from their experiments that 30% of the airborne bacteria fall directly from the air into the wound. The remaining 70% are indirectly transferred to the wound by the surgeons via the contaminated surrounding areas, such as drapes and instruments[130]. They calculated that in a conventionally-ventilated operating theatre, more than 95% of the bacteria found in the wound must have been transported by the airborne route. This was confirmed by Lidwell et al. during the Medical Research Council (MRC) trial[65], in which a definite relationship was demonstrated between air contamination and deep sepsis. In the trial, more than 8000 patients were allocated at random to conventional or ultraclean-air operating theatres. Significantly fewer cases of infection were found in clean-air systems, independent of the use of antibiotics[70].

Infection of the postoperative wound was an important risk factor for later deep infection. Deep infection occurred in 30% of the patients

with major postoperative wound infection, in 3% with suspected postoperative wound sepsis and in less than 1% without postoperative wound infection. Nevertheless, joint sepsis eventually developed in 60% of the patients without any postoperative woundhealing problems[69].
The incidence and type of bacteria found in operating theatre air, wounds and deep sepsis, were very similar, but some species, such as *S. aureus* and gram-negative bacteria, were more prevalent in deep sepsis. These bacteria are probably more virulent than others[85,86].
There is evidence that the source of superficial postoperative wound infection differs from that which leads to deep joint sepsis. In 71% of the cases of deep joint sepsis, a possible source could be matched by phage typing with the theatre staff present at the time of the operation. In the case of postoperative wound infections which did not progress to deep sepsis, only 21% of the theatre staff were implicated. Later contamination on the ward would seem to be the most likely cause of these superficial postoperative wound infections[66].
Sometimes infection is present before the operation. Latent infection can persist for decades in previously septic areas, but this is rarely the cause of deep infection in primary joint replacement[58]. In revision surgery, however, undiagnosed latent infection can cause a high percentage of septic failures[72].

Deep infection initiated after the operation

Deep infection initiated after surgery is caused by the haematogenous spread of bacteria from distant infections. The 'early' type of haematogenous infection occurs in the postoperative period[5]. It appears that there is increased susceptibility to haematogenous seeding from distant foci during the first 4 to 6 weeks after implantation[24,29,30,54,99,133]. Animal experiments have confirmed this postoperative susceptibility[7,36]. Concurrent infections should therefore be treated vigorously with antibiotics and other measures in order to prevent bacteraemia[7].
The 'late' type of haematogenous infection occurs in patients who have a long pain-free interval. After an intercurrent infection or an invasive procedure in a contaminated area, acute joint pain may develop with subsequent symptoms of deep infection[5].
Host factors as well as the amount and virulence of the bacteria play a role in the development of deep implant infection after bacteraemia, as not every bacteraemic episode leads to joint sepsis[24,32,116]. Patients with rheumatoid arthritis seem to be more susceptible to haematogenous infection[2,3,5,24,99]. Hinged knee prostheses are also a risk factor for acquiring haematogenous infection[3].
Transient, usually asymptomatic bacteraemia occurs in a wide variety

of procedures and manipulations, particularly those associated with trauma to the mucous membranes. Very high percentages of positive blood cultures are found following dental extractions, manipulation of the urogenital tract and septic foci[38,120].

The most frequent sources of haematogenous spread are cutaneous lesions, the respiratory tract, the urinary tract and the oral cavity[3,6], but the gut and other infected joints and prostheses have also been reported as sources[1,51,53,99,118,133]. The most frequent isolate (50%) was *S. aureus* and in 25% a gram-negative organism was found[3,6].

The risk of haematogenous infection was calculated for eight (mostly retrospective) series, comprising more than 1000 arthroplasties[2,17,39,40,57,99,109] (Table II). The results showed that an average of 18% of all deep infections were presumed to be caused by haematogenous infection. The contribution varied considerably within the different series, from 5 to 49%.

Table II Incidence of haematogenous infection

Author (ref.)	Type of arthroplasty	No. of patients n	Total infections n (%)	Haematogenous infections n (%)	Percentage of total %
Poss[99]	various	4240	53 (1.3)	26 (0.6)	49
Joselfson[57]	tha	1633	16 (1.0)	2 (0.1)	13
Glynn[40]	tha	1500	14 (0.9)	2 (0.1)	14
Fitzgerald[39]	tha	3215	42 (1.3)	7 (0.2)	17
Salvati[109]	tha/tka	3175	57 (1.8)	7 (0.2)	12
Carlsson[17]	tha	1065	73 (6.9)	4 (0.4)	5
Ainscow[2]	tha	1112	22 (2.0)	3 (0.3)	14
Total		15940	277 (1.7)	51 (0.3)	18

(tha = total hip arthroplasty, tka = total knee arthroplasty)

Lidwell[67] stated that the proportion of haematogenous infections must be very small, because his calculations on air contamination data revealed that at least 90% of the infections which manifested themselves in the first two years after the operation were initiated in the operating theatre; thus the contribution of haematogenous infection in this period was 10% or less. The incidence in Table II is somewhat higher.

Pathogenesis and the susceptibility to infection

Biomaterials, such as orthopaedic prostheses, provide a good adhesive surface for bacteria. Immediately after a prosthesis has been implanted,

the surface is covered by a layer of glycoproteins. In this layer, receptors are available which facilitate the adherence of tissue cells and bacteria. Both tissue cells and bacteria 'compete in the race for the surface', but the bacteria may defeat the tissue cells because they adhere more easily. After adherence has taken place, the bacteria immediately start to produce a form of slime, the glycocalyx, which has various functions, including rendering adherence irreversible, permitting the optimal concentration of nutrients and providing protection against external hazards, such as phagocytosis and antibiotics[22,41]. Glycocalyx formation is considered to be the natural mode of growth of bacteria, affording it the best chances for survival.

The primary local immune defense system reacts within two to five hours after the initial invasion of bacteria into the tissue. During this time, the infection is either localized and suppressed, or spreads to adjacent tissues[13,26,27,78,79]. This phase also constitutes the decisive period in which antibiotics are likely to be successful in reducing the total number of bacteria and enhancing the immune system. After this time the effect is very limited[8,13,26,27,79,113].

There are numerous factors which interfere with the optimal functioning of the local immune system. For example, poor blood flow and hypoxia reduce the efficacy of the immune defense reaction[75,78,97,108], malnutrition may reduce the synthesis of humoral factors and humoral immunity is also reduced in agammaglobulinaemia and c3 deficiency. The cellular immune system may be impaired by neutropaenia, rheumatoid arthritis, diabetes, alcohol consumption and various drugs, such as steroids and immuran[97,108].
The presence of a foreign body in itself may reduce the minimum infecting bacterial dose by up to a factor of 10.000[34]. The properties of biomaterials are important. Reactive material potentiates infection more seriously than non-reactive material[31,119].
The bone cement most frequently used nowadays significantly reduces the minimum infecting dose. The monomer which leaks from the resorbable plastic interferes with complement factors, chemotactic factors, the migration and viability of the leukocytes and impairs intracellular killing[90-95].
Certain metals used in implant surgery (nickel and cobalt) have a toxic effect on macrophages[101,102]. Leucocytes exposed to synovial fluid with metal wear debris from hinged knee prostheses show a depressed mitotic index, indicating cellular damage[23].

Prophylaxis

A considerable decrease in prosthesis-related infections can be achieved by reducing the bacterial inoculum during surgery. This can only be accomplished by preventing the deposition of bacteria into the wound, by means of asepsis and clean-air systems and by killing as many bacteria as possible using secondary measures, such as suitable antibiotics given perioperatively[86].

Clean air systems

The most effective method of preventing the deposition of bacteria into the wound is by reducing air contamination using clean-air systems, provided that asepsis and skin disinfection protocols are carefully followed. Very low airborne bacterial counts must be achieved in order to reduce bacterial deposition into the wound and subsequent sepsis[131].
Clean-air systems emit a rapid unidirectional flow of filtered sterile air over the operating area (100-300 times the operating theatre volume per hour). Full-walled downflow ventilation systems provide the lowest degree of air contamination, while partially-walled and horizontal systems are less effective[68].
Air contamination can be further diminished by reducing the bacterial dispersion of the theatre staff. This can be achieved with body-exhaust gowns, made of tightly woven bacterial-occlusive cloth. Promising experiments with nonwoven conventional disposable gowns in combination with nonwoven suits have shown an equivalent reduction in dispersion, without hampering communication or movement and with the same comfort as cotton gowns[68 82 131]. Mean values in modern operating theatres of 164 c.f.u./m^3 are reduced to less than 1 c.f.u./m^3 by full-walled downflow systems in combination with body exhaust suits[70].
In the MRC trial, ultraclean-air systems reduced the number of cases of confirmed sepsis by half, compared to conventional ventilation. When body-exhaust suits were worn, the reduction was almost fivefold[70]. Similar results were reported by Nelson[84], who also reviewed the literature.

Perioperative systemic antibiotics

Perioperative systemic antibiotics are a very effective means of reducing the incidence of prosthesis-related sepsis. In a large randomized clinical trial using cefazolin antibiotic prophylaxis versus a placebo, Hill et al.[47] found a sevenfold reduction in prosthesis-related infection. These patients underwent surgery in a conventional operating theatre. Ericson[37] also observed a sevenfold reduction using cloxacillin in a

smaller trial. In the treatment of hip fractures, a six to eightfold reduction has been reported[9,14,122].
In the MRC trial, Lidwell et al. found a three to fourfold reduction, but the antibiotics were not administered at random. They also found that the effects of clean air were supplementary to those achieved by the administration of antibiotics, resulting in a more than eightfold reduction in sepsis (from 3.4 to 0.3 percent). Thus deep implant infection can be limited to a few per thousand operations[70].
The choice of prophylactic antibiotic should be based on the current causative agents and the sensitivity patterns at the hospital. Narrow spectrum antistaphylococcal prophylaxis does not prevent an infection with gram-negative bacteria. When Lidwell et al. administered antistaphylococcal antibiotics, a greater incidence of gram-negative bacteria infections was observed than when broad spectrum antibiotics were used[66].
Second generation cephalosporins, such as cefuroxime and cefamandole, have become popular in prophylaxis owing to their wide activity against gram-negative bacteria, without losing their effectiveness against *staphylococci*. However, the cefalosporin spectrum has its limitations. These drugs are not sufficiently active against *P. aeruginosa*, *Enterobacter sp*, *S. faecalis* and anaerobes[115].
It is important that the antibiotics are given at the induction of anaesthesia and 10 minutes before the inflation of the tourniquet[56,62]. Intravenous injection is preferred, because this results in higher blood and tissue concentrations compared with intramuscular injection[10,74].
Prophylaxis can be short of duration, because trials have shown that there is no difference in the incidence of deep infection between 14-day and 1-day [98] or 5-day and 1-day antibiotic prophylaxis[83]. One-day prophylaxis is the accepted practice nowadays.
A further reduction to one perioperative dose is now being advocated for antibiotics with a sufficiently long half-life that provide high tissue concentrations during the operation[48,49]. A single dose has already proven to be effective in cardiac[21], abdominal[46,117] and gynaecological surgery[44,77]. We are currently investigating the safety of this approach in a controlled multicentre trial on joint replacement in more than 2500 patients. The results after one dose of cefuroxime prophylaxis are being compared to those after three doses.

Antibiotics in bone cement

After Buchholz and Engelbrecht reported on the effects of antibiotic-loaded bone cement[11], this product has been employed for prophylaxis, with gentamicin as the most commonly used drug. After implantation, high bone and soft tissue concentrations are achieved in the first 48

hours. Thereafter gentamicin may be eluted for a long period (months) in low concentrations[15,35,123,126].
Wannske and Tscherne[127] found that the infection rate was reduced from 5.9% to 1.2% when gentamicin-loaded cement was used, compared to plain cement and no systemic antibiotics. Josefsson et al.[80] compared systemic antibiotics to gentamicin cement and found a reduction from 1.6% to 0.4%. In the gentamicin cement group, they found more superficial infections, which indicates that wound tissue distant from the gentamicin cement is not sufficiently protected. Additional systemic antibiotics should therefore be used[124].
In a retrospective study, Lynch et al.[71] confirmed the efficacy of gentamicin cement above plain cement in patients who had undergone previous hip surgery and revisions, but no difference was found in patients with primary arthroplasties without previous surgery. A combined approach with systemic antibiotics and antibiotic-loaded cement seems to be justified in high-risk patients, but further clinical trials are needed[124].
Animal studies have confirmed the protective action of antibiotic-loaded cement against perioperative bacterial contamination[36,107,114], but no comparison has been made with systemic antibiotics. Protection against haematogenous infection was found in one study[36] in the immediate postoperative period but not after 6 weeks[6,36]. The intervening period was not evaluated, however.

Diagnosis

Clinical diagnoses

Pain is a prominent feature in prosthesis-related infections, affecting more than 80-90% of the patients with deep infection[15,53,80]. Constant pain at rest, aggravated on weight-bearing and gradually increasing after the operation, is suggestive of infection; a more sudden onset of pain suggests mechanical loosening[63,105]. Antibiotics may help to diminish the pain of infection, but do not cure chronic infection[61].
The symptoms of infection, such as increased temperature, warmth, redness and fistulization, are often less prominent[15,53,80]. Many patients with an infected arthroplasty admit that they were never entirely pain-free after the operation.

Laboratory investigations

Laboratory investigations can be of help, but it should be realized that negative results do not exclude infection. An elevated ESR of more than

35 mm is suggestive of, but does not prove, infection[19,57,55,105]. C-reactive protein is a more sensitive means for detecting infection[55,61,125].

Radiography and isotope scanning techniques

Serial radiographs showing periostial reactions, progressive radiolucent lines and cortical scalloping are suggestive of infection. These nonspecific signs can also be present in mechanical loosening, making differentiation difficult[4,16,87,111,112,128].

A technetium-99m (Tc-99m) bone scan may be helpful; intense uniform activity indicates infection, whereas mild local activity is more compatible with mechanical loosening[73,111,121]. The Tc-99m scan can be combined with a Gallium-67 scan. If an incongruent pattern is found, infection is likely, whereas congruent patterns favour mechanical failure[73,87,128]. Unfortunately, a number of scans fall into the gray zone between the extremes[43,87,111,112].

Another scanning technique is the injection of Indium-111 labelled autologous leucocytes, but this involves a very delicate technique for preparing the leucocyte-concentrates[80,100]. (Addendum: The utility of Indium-111 labeled immunoglobulin G is a new promising technique for identifying the presence, location, extent and soft tissue involvement of acute and low-grade bone infections. The sensitivity appears to be at least as high as that of labeled leucocytes and labeled immunoglobelin can easily be prepared. Van Oyen W.J.G., Claessens R.A.M.J., Van Horn J.R., Van der Meer J.W.M., Corstens F.H.M., Scintigraphic Detection of Bone and Joint Infections with Indium-111-labeled Nonspecific Polyclonal Human Immunoglobelin G., *The Journal of Nuclear Medicine, 31, 4*: 403-412, 1990)

Microbial diagnoses

Aspiration of the joint before surgery can be performed, but false negative and false positive cultures do occur[12,50,80,89,96]. Local anaesthetics and contrast media should not be introduced into the joint before aspiration because of their possible bactericidal and bacteriostatic properties[25,30,76,110].

A definitive diagnosis can only be made after a revision operation. The diagnosis can then be based on the results of multiple biopsy cultures (at least 3) from interface tissue, each taken with a different pair of sterile forceps[59]. Preoperative antibiotic therapy should be stopped two to three days prior to the operation and perioperative antibiotics should be given only after the sampling has been completed[66]. Specimens should be sent to the laboratory immediately to preserve any anaerobes[115] and the cultures should be incubated for 10 days[42]. Both solid and broth media

should be used, as broth encourages the growth of organisms present in small numbers[28], while a solid medium gives an indication of the inoculum size and the number of different species present.

Frozen sections

During a revision operation, a frozen section of interface tissue can provide reliable information as to whether or not sepsis is present[20,33,81]. Acute inflammatory changes of more than five polymorphonuclear leucocytes per high power field (x 500) or severe chronic (more than 50 lymphocytes) inflammation are highly suspicious of sepsis[20,81], but occasional false positive[20] and false negative results[104] have been reported[81,104]. Gram staining is of little use in the diagnosis of subacute prosthesis-related infection. It is very important to sample representative interface tissue.

Conclusions

Etiology

Almost any type of microorganism can give rise to prosthesis-related infection. Acrobic and anaerobic skin commensals play an important role. Most infections are initiated during the operation by airborne contamination with infectious skin scales originating from individuals in the operating theatre, although a small number are caused by the early (postoperative) and late haematogenous seeding of bacteria from distant foci. The glycocalyx, a slime layer produced by bacteria, plays a major role in the pathogenesis. Biomaterials and debris from wear, impair the local immune response in various ways.

Prophylaxis

Clean-air systems reduce the rate of infection by half; when used in combination with body-exhaust gowns an additional 25% reduction is achieved. Concurrent perioperative antibiotics result in a four to sixfold reduction.
The above-mentioned measures in combination with clean air, produce a supplementary effect, resulting in a few infections per thousand operations. Antibiotic-loaded cement is advised in high-risk patients, but further controlled trials are needed to evaluate the efficacy, especially in primary procedures.

In prosthesis-related infections, various tests including physical examination, preoperative laboratory tests e g ESR and C-reactive protein, serial radiography, isotope scanning techniques and aspiration cultures may be helpful, but they will never completely prove or exclude the existence of infection During a revision operation, a frozen section of the interface may assist with the diagnosis, but a definitive diagnosis can only be made on the basis of multiple biopsy cultures, for which special culturing techniques should be used

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References

1 Ahlberg A , Carlsson A S , Lindberg L , Hematogenous infection in total joint replacement *Clin Orth 137* 69-75, 1978
2 Ainscow D A P , Denham R A , The risk of haematogenous infection in total joint replacements *J Bone Joint Surg 66B* 580-582, 1984
3 Bengtson S , Blomgren G , Knutson K , Wigren A , Lidgren L , Hematogenous infection after knee arthroplasty *Acta Orthop Scand 58* 529-534, 1987
4 Bergstrom B , Lidgren L , Radiographic abnormalities caused by postoperative infection following total hip arthroplasty *Clin Orthop 99* 95-102, 1974
5 Bigham L U , Stinchfield F E , Hematogenous infections of total joint replacement In *Infections in joint replacement surgery* Ed Eftekhar N S , C V Mosby Co , St Louis, Toronto, 399-413, 1984
6 Blomgren G , Hematogenous infection of total joint replacement *Acta Orthop Scand* (Suppl 187) *52* 7-63, 1981
7 Blomgren G , Lindgren U , The susceptibility of total joint replacement to hematogenous infection in the early postoperative period *Clin Orthop 151* 308-312, 1980
8 Bowers W H , Wilson J C , Greene W B , Antibiotic prophylaxis in experimental bone infections *J Bone Joint Surg 55A* 795-807, 1973
9 Boyd J , Burke J I , Colton T , A double-blind clinical trial of prophylactic antibiotics in hip fractures *J Bone Joint Surg 55A* 1251-1258, 1973
10 Browning A K , House C A , Pharmacokinetics of cefuroxime, compared to other cephalosporins *Proc of the Roy Soc Med* (Int Congress and Symposium) *38* 87-99, 1978
11 Buchholz H W , Engelbrecht H , Uber die Depotwirkung einiger Antibiotica bei Vermischung mit dem Kunstharz Palacos *Der Chirurg 11* 511-515, 1970
12 Buchholz H W , Elson R A , Engelbrecht E , Lodenkamper H , Rottger J , Siegel A , Management of deep infection of total hip replacement *J Bone Joint Surg 63B* 342-353, 1981
13 Burke J F , The effective period of preventive antibiotic action in experimental incisions and dermal lesions *Surgery 50* 161 168, 1961
14 Burnett J W , Gustilo R B , Williams D N , Kind A C , Prophylactic antibiotics in hip fractures *J Bone Joint Surg 62A* 457-461, 1980
15 Callaghan J J , Salvati E A , Brause B D , Rimnac C M ,Wright T , Reimplanta-

tion for salvage of the infected hip Rationale for the use of gentamicin-impregnated cement and beads In *The Hip Society, Proceedings of the thirteenth open Scientific Meeting of the Hip Society* Ed C V Mosby Co , St Louis, Toronto, 65-94, 1985
16 Carlsson A S , Egund N , Gentz C , Hussenius A , Josefsson G , Lindberg L , Radiographic loosening after revision with gentamicin-containing cement for deep infection in total hip arthroplasties *Clin Orthop* 194 271-279, 1985
17 Carlsson A S , Lidgren L , Prophylactic antibiotics against early and late deep infections after total hip replacements *Acta Orthop Scand 48* 405-410, 1977
18 Carlsson A S , Josefsson G , Lindberg L , Revision with gentamicin-impregnated cement for deep infections in total hip arthroplasties *J Bone Joint Surg 60A* 1059-1064, 1978
19 Carlsson A S , Erythrocyte sedimentation rate in infected and non-infected total hip arthroplasties *Acta Orthop Scand 49* 287-290, 1978
20 Charosky C B , Bullough P G , Wilson P D , Total hip replacement failures *J Bone Joint Surg 55A* 49-58, 1973
21 Conte J L , Cohen S N , Roe B B , Elashoff R M , A prospective double-blind comparison of single-dose versus multiple-dose regimens *Ann Int Med 76* 943-949, 1972
22 Costerton J W , Cheng K J , Geesey G G , Ladd T I , Nickel J C , Dasgupta M , Marrie I H J , Bacterial biofilms in nature and diseases *Ann Rev Microbiol 41* 435-464, 1987
23 Crachiolo A , A quantitative analysis of metal levels in synovial fluids and synovium of patients with joint replacement and the effect of these metals on cellular function *Orthop Trans 4* 218, 1980
24 D'Ambrosia R D , Heater R , Secondarily infected total joint replacements by hematogenous spread *J Bone Joint Surg 58A* 450-453, 1976
25 Dawson P , Becker A , Holton J M , The effect of contrast media on the growth of bacteria *Brit J Radiol 56* 809-815, 1983
26 Dineen P , A period of unusual microbial susceptibility in an experimental staphylococcal infection *J Infect Dis 108* 174-180, 1961
27 Dineen P , Further studies on the period of microbial susceptibility *J Infect Dis 111* 169-174, 1962
28 Dingeldein L , Bacteriology Culture techniques *Revision Arthroplasty 2 16-19*, Proceedings symposium Harrogate, England, 2-4 March 1983
29 Donovan I H L , Gordon R O , Nagel D A , Urinary infections in total hip arthroplasty *J Bone Joint Surg 58A* 1134-1137, 1976
30 Dory M A , Wautelet M J , Arthroscopy in septic arthritis lidocaine and iodine containing contrast media are bacteriostatic *Arthritis and Rheumatism 28* 198-203, 1985
31 Doucherty S H , Simmons R L , Infections in bionic man the pathobiology of infections in prosthetic devices-part 1, *Year Book Medical Publishers Inc* Chicago, 218-264, 1982
32 Downes L M , Late infection after total hip replacement *J Bone Joint Surg 59B* 42-44, 1977
34 Elek S D , Cohen P E , The virulence of *Staphylococcus pyogenes* for man A study of the problems of wound infection *Br J Exp Path 38* 573-586, 1957
35 Elson R A , Jephcott A E , McGeghie D B , Verettas D , Antibioticloaded acrylic cement *J Bone Joint Surg 59B* 200-205, 1977
36 Elson R A , Jephcott A E , McGeghie D B , Verettas D , Bacterial infection and acrylic cement in the rat *J Bone Joint Surg 59B* 452-457, 1977
37 Ericson C , Lidgren L , Cloxacillin in the prophylaxis of postoperative infections of the hip *J Bone Joint Surg 55A* 808-813, 1973

38. Everett E., Hirschmann J.V., Transient bacteremia and endocarditis prophylaxis. A review. *Medicine. 56:* 61-77, 1977.
39. Fitzgerald R.H., Nolan D R., Ilstrup D.M., Van Scoy R.E., Washington J.A., Coventry M.B., Deep wound sepsis following total hip arthroplasty. *J. Bone Joint Surg. 59A*: 847-855, 1977.
40. Glynn M.K., Sheehan J.M., An analysis of the causes of deep infection after hip and knee arthroplasties. *Clin Orthop. 178*: 202-207, 1983.
41. Gristina A.G., Biomaterial-centered infection: Microbial adhesion versus tissue integration. *Science 237*: 1588-95, 1987.
42. Gristina A.G., Costerton J.W., Bacterial adherence and the glycocalyx and their role in musculoskeletal infection. *Orthop. Clin. N. Am. 15*: 517-535, 1984.
43. Gristina A.G., Koldin J., Current concepts review, total joint replacement and sepsis. *J. Bone Joint Surg. 65A*: 128-134, 1983.
44. Hamod K.A., Spence M.R., Rosenshein N.B., Dillon M.B., Single-dose and multidose prophylaxis in vaginal hysterectomy: a comparison of sodium cephalothin and metronidazole. *Am. J. Obst. Gyn. 136*: 976-979, 1980.
45. Hardinge K., Revision of infected total hip replacement. *Sem. Orthop. 1*: 49-63, 1986.
46. Higgins A.F., Lewis A., None P., Hole M.L., Single and multiple dose cotrimoxazole and metronidazole in colorectal surgery. *Brit. J. Surg. 67*: 90-92, 1980.
47. Hill C., Mazas F., Flamant R., Evrard J., Prophylactic cefazolin versus placebo in total hip replacement. *Lancet 1*: 795-797, 1981.
48. Hirschmann J.V., Inui T.S., Antimicrobial prophylaxis: A critique of recent trials. *Rev. Inf. Dis.2*: 1-23, 1980.
49. Hirschmann J.V., Antibiotics in the prevention of infection associated with prosthetic devices In: *Infection associated with Prosthetic Devices.* Ed. Sugarman B.S., Young E.J., CRC-Press , 270-277, 1984.
50. Hughes P.W., Salvati E.A., Wilson P.D., Blumenfeld E.L., Treatment of subacute sepsis of the hip by antibiotics and joint replacement. Criteria for diagnosis with evaluation of twenty-six cases. *Clin.Orthop. 141*: 143-157, 1979.
51. Hunter G.A., Dandy D., Diagnosis and natural history of the infected total hip replacement. In: *The Hip Society, Proceedings of the thirteenth open Scientific Meeting of the Hip Society.* Ed. C.V. Mosby Co., St.Louis,Toronto, 176-192, 1977.
52. Hunter G.A., Welsh R.P., Cameron H.U., Bailey W.H., The results of revision of total hip arthroplasty. *J.Bone Joint Surg. 61B*: 419-421, 1979.
53. Inman R.D., Gallegos K.V., Brause B.D., Redecha P.B., Christian C.L., Clinical and microbial features of prosthetic joint infection. *Am. J. Med. 77*: 47-53, 1984.
54. Irvine R., Johnson B.L., Amstutz H.C., The relationship of genitourinary tract procedures and deep sepsis after total hip replacement. *Surg. Gyn. Obstet. 139:* 701-706, 1974.
55. Jenny G., Schaub J M., Ferard G., Metais P., Kempf L., Interet du dosage de la C-reactive proteine dans l'infection osteoarticulaire. *Rev. Chir. Orthop. 72:* 197-201, 1986.
56. Johnson D.P., Antibiotic prophylaxis with cefuroxime in arthroplasty of the knee. *J. Bone Joint Surg. 69B:* 787-789, 1987.
57. Josefsson G., Lindberg L., Wiklander B., Systemic antibiotics and gentamicin-containing bone cement in the prophylaxis of postoperative infections in total hip arthroplasty. *Clin. Orthop. 159*: 194-201, 1981.
58. Jupiter J.B., Karchmer A.W., Drennan Lowell J., Harris W.H., Total hip arthroplasty in the treatment of adult hips with current or quiescent sepsis. *J. Bone Joint Surg. 63A:* 194-200, 1981.
59. Kamme C., Lindberg L., Aerobic and anaerobic bacteria in deep infections after total hip arthroplasty. *Clin. Orthop. 154:* 201-207, 1981.

60. Kamme C., Lidgren L., Lindberg L., Mardh P., Anaerobic bacteria in late infections after total hip arthroplasty. *Scand. J. Infect. 6:* 161-165, 1974.
61. Grover M.L., Shearer J.R., Ainscow D.A.P., The acute-phase response of plasma proteins as an aid to the diagnosis of infections in joint replacements. *J. Bone Joint Surg. 68B*: 157, 1987.
62. Katz J.F., Siffert R.S., Basic science and pathology: Tissue antibiotic levels with tourniquet use in orthopedic surgery. *Clin. Orthop. 165*: 261-265, 1982.
63. Klenerman L., The management of the infected endoprothesis. Review. *J.Bone Joint Surg. 66B*: 645-651, 1984.
64. Lidgren L., Carlsson A., Lindberg L., Antibiotikabehandlung bei Infizierten Totalen Gelenkplastiken. *Orthop. Praxis.13*: 344-347, 1977.
65. Lidwell O.M., Lowbury E.J.L., Whyte W., Blowers R., Stanley S.J., Lowe D., Airborne contamination of wounds in joint replacement operations: The relationship to sepsis rates. *J. Hosp. Inf. 4*: 111-131, 1983.
66. Lidwell O.M., Lowbury E.J.L., Whyte W., Blowers R., Stanley S.J., Lowe D., Bacteria isolated from deep joint sepsis after operation for total hip or knee replacement and the sources of the infections with Staphylococcus aureus. *J.Hosp.Inf. 4*: 19-29, 1983.
67. Lidwell O.M., The operating environment. *Sem. Orthop. 1*: 33-40, 1986.
68. Lidwell O.M., Clean air at operation and subsequent sepsis in the joint. *Clin. Orthop. 211: 91-102, 1986.*
69. Lidwell O.M., Lowbury E.J.L., Whyte W., Blowers R., Stanley S.J., Lowe D., Infection and sepsis after operations for total hip or knee joint replacement: Influence of ultraclean air, profylactic antibiotics and other factors. *J. Hyg. Cambr. 93:* 504-529, 1984.
70. Lidwell O.M., Lowbury E.J L., Whyte W., Blowers R., Stanley S.J., Lowe D., Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement: A randomised study. *Brit. Med. J. 285:* 10-14, 1982.
71. Lynch M., Esser M.P., Shelley P., Wroblewski B.M., Deep infection in Charnley low-friction arthroplasty: Comparison of plain and gentamicin-loaded cement. *J. Bone Joint Surg. 69B:* 355-360, 1987.
73. Lyons C.W., Berquist T.H., Lyons J.C., Rand J.A., Brown M.L., Evaluation of radiographic findings in painful hip arthroplasties. *Clin. Orthop. 195:* 239-251, 1985.
74. Mader J.T., Cierny G., The principles of the use of preventive antibiotics. *Clin. Orthop. 190:* 75-82, 1984.
75. Marks K.E., Factors controlling the rate of osteomyelitis in rabbit tibia following simulated total joint replacement. *Orthop. Trans. 4:* 175-176, 1984.
76. Melson G.L., McDaniel R.C., Southern P.M., Staple T.W., In vitro effects of iodinated arthographic contrast media on bacterial growth. *Diag. Radiol. 112:* 593-596, 1974.
77. Mendelson J., Portnoy J., Saint de Victor J.R., Gelfand M.M. Effect of single and multidose cephradine prophylaxis on infectious morbidity of vaginal hysterectomy. *Obst. Gynecol. 53:* 31-35, 1979.
78. Miles A.A., The inflammatory response in relation to local infections. *Surg.Clin.N. Am. 60:* 93-105, 1980.
79. Miles A.A., Miles E.M., Burke J., The value and duration of defense reactions of the skin to the primary lodgement of bacteria. *Br. J. Exp. Pathol. 38:* 79-96, 1957.
80. Miley G.B., Scheller A.D., Turner R.H., Medical and surgical treatment of the septic hip with one-stage revision arthroplasty. *Clin. Orthop. 170:* 76-82, 1982.
81. Mirra J.M., Amstutz H.C., Matos M., Gold R., The pathology of the joint tissues and its clinical relevance in prosthesis failure. *Clin. Orthop. 117:* 221-240, 1976.

82. Mitchel N.J., Evans D.S., Kerr A., Reduction of skin bacteria in theatre air with comfortable, nonwoven disposable clothing for operating theatre staff. *Brit. Med. J. 1:* 696-698. 1978.
83. Nelson C.L., Green T.G., Porter R.A., Warren R.D., One day versus seven days of preventive antibiotic therapy in orthopedic surgery. *Clin. Orthop. 176:* 258-263, 1983.
84. Nelson J.P., Operating room environment: Clean rooms and personnel-isolator systems. In: *Infection in joint replacement surgery.* Ed. Eftekhar N.S., C.V. Mosby Co., St.Louis, Toronto, 167-178, 1984.
85. Nelson J.P., The operating room environment and its influence on deep wound infection. In: *The Hip Society, Proceedings of the fifth open Scientific Meeting of the Hip Society.* Ed. C.V. Mosby Co., St.Louis, Toronto, 129-146, 1977.
86. Nelson J.P., Observations on the prevention and treatment of THA deep sepsis. In: *The Hip Society, Proceedings of the twelveth open Scientific Meeting of the Hip Society.* Ed. C.V. Mosby Co., St.Louis,Toronto, 359-364, 1984.
87. Norris S.H., Investigation of Total Joint Replacement. *Sem.Orthop. 1:* 41-48, 1986.
88. Ouzounian T.J., Thompson L., Grogan T.H.J., Webber M.M., Amstutz H.C. Evaluation of musculoskeletal sepsis with indium-111 white blood cell imaging. *Clin. Orthop. 221:* 304-311, 1987.
89. Patel D., Karchmer A., Harris W., Role of preoperative aspiration of the hip prior to total hip replacement. In: *The Hip Society, Proceedings of the fourth open Scientific Meeting of the Hip Society.* Ed. C.V.Mosby Co., St.Louis,Toronto, 219-223, 1976.
90. Petty W., The effect of methylmethacrylate on bacterial phagocystosis and killing by human polymorphonuclear leukocytes. *J. Bone Joint Surg. 60A:* 752-757, 1978.
91. Petty W., The effect of methylmethacrylate on chemotaxis of polymorphonuclear leukocytes. *J. Bone Joint Surg. 60A:* 492-498, 1978.
92. Petty W., The effect of methylmethacrylate on the bacterial inhibiting properties of normal human serum. *Clin. Orthop. 132:* 266-278, 1978.
93. Petty W., Calswell J.R., The effect of methylmethacrylate on complement activity. *Clin. Orthop. 128:* 354-360, 1977.
94. Petty W., Spanier S., Shuster J.J., Silverthorne C., The influence of skeletal implants on incidence of infection. *J. Bone Joint Surg. 67A:* 1236-1244, 1985.
95. Petty W., Spanier S., Silverthorne C., The influence of skeletal implant on infection. *Orthop. Trans. 4:* 367, 1984.
96. Phillips W.C., Kattapuram S.V., Efficacy of preoperative hip aspiration performed in the radiology department. *Clin. Orthop. 179:* 141-146, 1983.
97. Polk H.C., Fry D., Flint L.M., Dissemination and causes of infection. *Surg. Clin. N. Am. 56.* 817-829, 1976.
98. Pollard P., Hughes S.P.F., Scott J E., Evans M.J., Benson M.K.D., Antibiotic prophylaxis in total hip replacement. *Brit. Med. J. 1:* 707-709, 1979.
99. Poss R., Thornhill T.H.S., Ewald F.C., Thomas W.H., Batte N.J., Sledge C.B., Factors influencing the incidence and outcome of infection following total joint arthroplasty. *Clin. Orthop.* 182: 117-127, 1984.
100. Pring D.J., Henderson R.G., Rivett A.G., Krausz T., Coombs R.R.H., Lavender J.P., Autologous granulocyte scanning of painful prosthetic joints. *J. Bone Joint Surg. 68B:* 647-652, 1986.
101. Rae T., The toxicity of metals used in orthopaedic prostheses. *J. Bone Joint Surg. 63B:* 435-440, 1981.
102. Rae T., A study on the effects of particulate metals of orthopaedic interest on murine macrophages in vitro. *J. Bone Joint Surg. 57B:* 444-451, 1975.
103. Rand J.A., Morrey B.F., Bryan R.S., Management of the infected total joint arthroplasty. *Orthop. Clin. N. Am. 15.* 491-504, 1984.

104. Rand J.A., Bryan R.S., Reimplantation for the salvage of an infected total knee arthroplasty. *J. Bone Joint Surg. 65A:* 1081-1086, 1983.
105. Rens Th.J.G. van, Slooff T.J.J.H., The investigation of the painful total hip. In: *Complications of total hip replacement.* Ed. Ling R.S.M., Churchill Livingstone, 231-241, 1984.
106. Ritter M.A., Ecology of the operating room. In: *Infection in joint replacement surgery,* Ed. Eftekhar N.S., C.V. Mosby Co., St.Louis, Toronto, 131-148, 1984.
107. Rodeheaver G.T., Rukstalis D., Bono M., Bellamy W., A new model of bone infection used to evaluate the efficacy of antibiotic-impregnated polymethylmethacrylate cement. *Clin. Orthop. 178:* 303-311, 1983.
108. Ryan G.B., Inflammation and localization of infection. *Surg. Clin. NAm. 56:* 831-846, 1976.
109. Salvati E.A., Robinson R.P., Zeno S.M., Koslin B.L., Brause B.D., Wilson P.D., Infection rates after 3175 total hip and total knee replacements performed with and without a horizontal unidirectional filtered air-flow system. *J. Bone Joint Surg. 64A*: 525-535, 1982.
110. Schmidt R.M., Rosenkrantz H.S., Antimicrobial activity of local anesthetics: lidocaine and procaine. *J. Inf. Dis. 121*: 597-607, 1970.
111. Schneider R., Soudry M., Radiographic and scintigraphic evaluation of total knee arthroplasty. *Clin. Orthop. 205*: 108-120, 1986.
112. Schneider R., Freiberger R.H., Ghelman B., Ranawat C.S., Radiologic evaluation of painful joint prostheses. *Clin. Orthop. 170:* 156-168, 1982.
113. Schurman D.J., Use of systemic antibiotics in total joint replacement. In: *Infection in total joint replacement.* Ed. Eftekhar N.S., C.V. Mosby Co., St.Louis, Toronto, 236-249, 1984.
114 Schurman D.J., Trindade C., Hirshman H P., Moser K , Kajiyama G., Stevens P., Antibiotic-acrylic bone cement composites: studies of gentamicin and palacos. *J. Bone Joint Surg. 60A:* 978-984, 1978.
115. Speller D.C.E., Microbiology of infected joint protheses. *Sem. Orthop. 1:* 1-9, 1986.
116. Stinchfield F.E., Bigliani L.U., Neu H.C., Goss TH.P., Foster C.R., Late hematogenous infection of total joint replacement. *J. Bone Joint Surg. 62A:* 1345-1350, 1980.
117. Stone H.H., Haney B.B., Kolb L.D., Geneber C.E., Hooper C.A., Prophylactic and preventive antibiotic therapy: timing, duration and economics. *Ann. Surg. 189:* 691-699, 1979.
118. Strazzeri J.C., Anzel S., Infected total hip arthroplasty due to Actinomyces israelii after dental extraction. *Clin. Orthop. 210*: 128-131, 1986.
119. Sugarman B., Infections associated with often-used surgical material.in: *Infections associated with prosthetic devices.* Ed. Sugarman B.S. and Young E.J., CRC-Press, 12-22, 1984.
120. Sullivan N.M., Sutter V.L., Mims M.M., Marsh V.H., Finegold S.M., Clinical aspects of bacteremia after manipulation of the genitourinary tract. *J. Inf. Dis. 127:* 49-55, 1973.
121. Tehranzadeh J., Schneider R., Freiberger R.H., Radiological evaluation of painful total hip replacement. *Diagn. Radiol. 141:* 355-362, 1981.
122. Tengve B., Kjellander J., Antibiotic prophylaxis in operations on trochanteric femoral fractures. *J. Bone Joint Surg. 60A:* 97-99, 1978.
123. Torholm C., Lidgren L., Lindberg L., Kahlmeter G., Total hip joint arthroplasty with gentamicin-impregnated cement. *Clin. Orthop. 181:* 99-106, 1983.
124. Trippel S.B., Antibiotic-impregnated cement in total joint arthroplasty: current concepts review. *J. Bone Joint Surg. 68A:* 1297-1302, 1986.
125. Leeuwen van M.A., Rijswijk M.H., Westra J., Jong de H.J., Marring J., C-Reac-

tieve proteine; Een dure bezinking? *Ned. Tydschr. Geneeskd. 130:* 1391-1395, 1986.
126. Wahlig H., Dingeldein E., Buchholz H.W., Buchholz M., Bachmann F., Pharmacokinetic study of gentamicin-loaded cement in total hip replacements: comparative effects of varying dosage. *J. Bone Joint Surg. 66B:* 175-179, 1984.
127. Wannske M., Tscherne H., Ergebnisse Prophylaktischer Anwendung von Refobacin-Palacos bei der Implantation von Endoprothesen des Huftgelenkes. *Aktuel Probl. Chir. Orth. 12:* 201-205, 1979.
128. Wetzner S.M., Newberg A.H., McKenzie J.D., Radiographic evaluation of the symptomatic hip replacement. In: *Revision Total Hip Arthroplasty.* Ed. Turner R.H., Scheller A.D.,Grune and Stratton, 25-48, 1982.
129. Whyte W., Vesley D., Hodgson R., Bacterial dispersion in relation to operating room clothing. *J. Hyg. Cambr. 76:* 367-379, 1976.
130. Whyte W., Hodgson R. Tinkler J., The importance of airborne bacterial contamination of wounds. *J. Hosp. Inf. 3:* 123-135, 1982.
131. Whyte W., Bailey P.V., Hamblen D.L., Fisher W.D., Kelly I.G., A bacteriologically occlusive clothing system for use in the operating room. *J. Bone Joint Surg. 65B:* 502-506, 1983.
132. Whyte W., Hodgson R., Tinkler J., Graham J., The isolation of bacteria of low pathogenicity from faulty orthopaedic implants. *J. Hosp. Inf. 2:* 219-230, 1981.
133. Wroblewski B.M., Del Sel H.J., Urethral instrumentation and deep sepsis in total hip replacement. *Clin. Orthop. 146:* 208-212, 1980.

Chapter III

Joint sepsis after propylaxis with one or three doses of cefuroxime in 2651 hip replacements

A randomized controlled multicentre trial

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Summary

The efficacy of infection prophylaxis in hip replacement with one perioperative dose of cefuroxime was evaluated in a randomized controlled multicentre study, using a three dose regimen as a control. All the operations were performed in conventionally-ventilated operating theatres. Of the 2796 hip replacements that entered in the study, 145 replacements were excluded due to protocol deviations. The remaining 2651 hip replacement were analysed: 1327 and 1324 in the one and three dose group, respectively.

There were no differences between the one dose group and the three dose group regarding the incidences of postoperative woundhealing problems, urinary tract or other distant infections. The use of additional antibiotics prescribed after the perioperative prophylaxis, did not differ either between the treatment groups.

After a mean follow-up of 13 months, joint sepsis was diagnosed in 11 of the patients in the one dose group (0.83%, 95% confidence limits 0.33-1 32%) and in 6 of the patients in the control group (0.45%, 95% confidence limits 0.08-0.81%). This difference was not significant (one tailed chi-square test, $p > 0.05$). The estimated difference between the one dose and three dose groups was 0.38% (95% confidence upper limit 0.9%). Therefore, it could not be confirmed that the efficacy of one dose was equal to that of three doses. However, the incidence of joint sepsis in this study was too small to draw definite conclusions. An extended follow-up, with probably more cases of joint sepsis, may provide more concluswe data. Until then a three dose regimen is recommended.

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Introduction

Perioperative systemic antibiotics in hip replacement form a very effective means of reducing the incidence of joint sepsis[1-4]. There is, however, no consensus on the optimal duration of antibiotic prophylaxis in joint replacement[5-8]. A duration of 24 hours is currently recommended in joint replacement surgery[9], but there is a trend towards further reduction to a single dose in orthopaedics[6,8,10] as well as in other surgical fields[11,12].
In order to establish the efficacy of a single perioperative antibiotic dose for infection prophylaxis in joint replacement surgery, a randomized controlled multicentre study was performed. Cefuroxime, a second generation cephalosporin with a half-life of 70 minutes, was chosen because this antibiotic provides a broad spectrum of activity against the organisms which cause joint sepsis in orthopaedic implants[13].

Patients and methods

Assuming that the incidence of joint sepsis is 1% with a three dose regimen, we estimated that at least 1250 patients were needed in each treatment group to detect a difference of 1% joint sepsis, on the basis of a one-sided type I error of 5% and a type II error of less than 20% (one-tail test). A difference of less than 1% (which is less than twice the incidence in the three dose regimen) would mean that the single dose was equally effective.
A study population of 1250 hip replacements per treatment group was sufficient to ensure that the upper 95% confidence limit (one-sided) for the difference between joint sepsis rates was almost certainly smaller than 1% (80% probability), given a joint sepsis rate of 1% in both groups[14].
Using these criteria, only rather large relative differences can be detected, but given the low incidence of joint sepsis, a detectable difference of 1% was considered to be adequate for estimating the efficacy of a single dose. If we were to employ a smaller detectable difference, the trial would require several thousands of operations more in each arm, which is impracticable.

Twenty-seven Dutch hospitals participated in the study from 1 July 1986 to 1 July 1988. Only centres with conventionally-ventilated operating theatres took part and local ethical committees approved the protocol.

Patients undergoing total hip replacement, hemi-arthroplasty of the hip

or total knee replacement were eligible for inclusion in the study. The exclusion criteria were allergy to cephalosporin, penicillin anaphylaxis, the use of antibiotics less than 48 hours before the operation, the use of perioperative antibiotics other than cefuroxime, malignancy in the operated joint, former or current sepsis in the joint and the use of gentamicin-impregnated bone cement for fixation of the prosthesis components.
Randomization of the prophylaxis regimen was performed using a computerized list in blocks of ten numbers. For every eligible patient, an envelope containing a self-adhesive label with the prescribed dosage, was opened sequentially. The label was placed on the patient records and anaesthesia list. Thus the treatment was not blinded. For logistic reasons, a number of centres randomized all the patients and exclusions were performed after the operation.

Cefuroxime at a dose of 1500 mg was administered intravenously to both groups at the induction of anaesthesia, 30 minutes before the first incision. In the three dose group, a second and third injection of 750 mg cefuroxime was given after 8 and 16 hours. Three centres rinsed the wound with a fluid containing an antibiotic; 2 centres used povidone iodine to rinse the wound.

Definitions

The clinical end point of the study was joint sepsis, reoperation or death.
- Confirmed joint sepsis was defined as a positive bacteriological culture at reoperation or a draining sinus. Strong evidence of sepsis was defined as four or more 'possible signs of infection'. These two groups of conditions were analysed together (category I).
- In patients who only showed two or three possible signs of sepsis (category II) a definite diagnosis could not be made. Patients with one or no signs (category III) were not suspected of having joint sepsis.

The conditions which were defined as being possible signs of infection at follow-up were: pain during weight-bearing and/or at rest, tenderness of the wound, fever, an abnormal X-ray (periostial reactions, progressive bone resorption), an increased ESR (more than 20 mm above the preoperative value or > 35 mm), positive culture in the joint fluid aspiration, a positive arthrogram, a bone scan showing the typical signs of infection or an increased C-reactive protein.

- Wound infection in the postoperative period, was defined as erythema more than one centimetre from the incision.
- Minor postoperative woundhealing problems were defined as erythema of the wound less than one centimetre from the incision, pus suture, small wound dehiscence, necrosis of the wound edge and blisters.
- Distant infections were usually diagnosed on the basis of positive cultures. A urinary tract infection was defined as bacteriuria of more than 10^5 bacteria/ml. Blood cultures of *Staphylococcus epidermidis* were only considered positive when cultured at least twice. A few lung, skin and other infections were diagnosed clinically.

Additional antibiotics prescribed after the perioperative period for wound and/or distant infections or other reasons, were also recorded. The amount of antibiotic was expressed in Defined Daily Doses which is based on the main indication and expressed as the weight of active substance[15].

Patients undergoing total knee replacement surgery were also eligible for inclusion in the study and were stratified by the randomization procedure. A total of 455 operations were registered, 58 of which were excluded (12.7%) and 35 withdrawn (8.8%), leaving 362 operations (328 patients) for analysis. Joint sepsis was diagnosed by follow-up in 3 out of the 175 (1.7%) operations in the single dose group and in 6 out of the 187 operations (3.2%) in the three dose group. As these data differed considerably from those obtained from the hip operations, the knee arthroplasties cohort was analysed separately.

The primary variable was joint sepsis (category I). Confidence limits (one-sided) were calculated for the differences, i.e. the ratio of the crude rates in both groups. Other outcome variables were compared by using a chi-square test (two-sided) with continuity correction.

Results

From 1 July 1986 to 1 July 1988, 3074 operations were registered. A total of 278 (9%) operations did not meet the criteria in the protocol and were excluded. The most frequent reason for exclusion was the use of gentamicin bone cement, which was often used in high risk patients. A number of centres did not enter their high risk patients in the study or they used gentamicin bone cement whereas other hospitals entered all the consecutive patients.

From the remaining 2796 operations, 145 (5%) were withdrawn, leaving 2651 operations (2547 patients) for analysis (Table I). A separate follow-up of all withdrawn patients showed that all were free from joint sepsis. Data on 15 patients were lost during follow-up. The mean follow-up duration was 13 months for both prophylaxis groups.

Table I Inclusion criteria, exclusions and withdrawals (hip replacements)

	Number of operations		
	one dose	three doses	total
RANDOMIZED	1600	1599	3199
OPERATIONS registered #	1540	1534	3074
EXCLUSIONS protocol	141 (9 2%)	137 (8 9%)	278 (9%)
FOLLOW-UP	1399	1397	2796
WITHDRAWN FROM ANALYSIS	72 (5 1%)	73 (5 2%)	145 (5 2%)
other type of antibiotic	17	16	33
died within 7 days	4	8	12
wrong dose or administration	42	35	77
second hip replacement ##	9	14	23
SUITABLE FOR ANALYSIS	1327	1324	2651

(# = in some patients, the operation was cancelled or a different procedure was performed, ## = during one hospital admission)

The two trial arms were well-matched with respect to the general and orthopaedic diagnoses (Table II). The incidence of rheumatoid arthritis, diabetes, use of steroids and prosthesis failure, was low. With respect to the data on the operative procedure, there were no relevant differences between the groups.

Joint sepsis was recorded in 11 patients (0.83%, 95% confidence limits 0.33-1.32) in the one dose group and in 6 patients (0.45%, 95% confidence limits 0.08-0.81) in the three dose group (Table III). This difference was not significant ($p < 0.05$, one tailed chi-square test). The estimated difference in incidence of sepsis between the one and three dose group was 0.38% (95% upper confidence limit 0.9%). The estimated ratio was 1.83 with an upper confidence limit of 4.2.
Joint sepsis was confirmed by a positive culture at reoperation and/or a draining sinus in fourteen patients. Three patients showed strong evidence of joint sepsis, of whom two underwent reoperation for infection, but their perioperative cultures were negative. The joint aspirate from the third patient was found to contain *Staphylococcus aureus.*

Table II General and orthopaedic characteristics (hip replacements)

	one dose n=1327	three doses n=1324
mean age yr SD)	69 1 (10 7)	69 1 (10 5)
sex - male/female	287/1040	266/1058
operated side - left/right	649/678	611/713
mean quetelet index kg/m2 (SD) [mv]	26 2 (3 8)[216]	26 5 (4 0)[220]
physical condition (moderate/poor)	206/19	184/17
steroid use	36	33
diabetes #	42	58
cardiac disease #	191	171
pulmonary disease #	86	87
preoperative infections	64	67
no concurrent diseases #	823	843
DIAGNOSIS		
osteoarthritis	959	954
rheumatoid arthritis	83	77
fracture (recent)	138	120
other	35	31
failed prosthesis	26	40
osteotomy	42	56
fracture osteosynthesis	33	30
other earlier operations	11	16
TYPE OF REPLACEMENT AND USE OF BONE CEMENT		
total hip cement a+ f+	863	859
a- f+	164	152
a+ f-	4	4
a- f-	183	188
hemiarthroplasty +/-	79/8	71/10
revisions (various procedures)	26	40
approach -(antero)lateral/posterolateral	439/888	422/902
surgeon status -staff/resident	1245/82	1242/82
mean blood loss in ml (SD [mv]	686 (422)[55]	705 482)[37]
mean operation time in minutes SD)[mv]	88 (31)[28]	89 (32)[16]
breakdown of sterility (>90% hole in glove)	75	82

((SD) = Standard Deviation, [mv] = number of missing values, a = acetabular component, f = femoral component, + = fixation with bone cement, - = fixation without bone cement, # = more than one concurrent illness possible)

Nine patients were diagnosed as having joint sepsis within one month after surgery. Five of these patients underwent early reoperation, comprising the evacuation of an infected haematoma or the excision of a sinus; four of these patients were functioning well at one year follow-up without signs of joint sepsis. One case of joint sepsis was diagnosed after

four months, one after five months, two after 11 months, two after 14 months, one after 18 and one after 24 months. There were two sepsis-related deaths, one in each prophylaxis group, after one month (one dose group) and after five months (three dose group).
At the five centres where the wound was rinsed during the operation with a fluid containing an antibiotic or povidone iodine, the incidences of joint sepsis were similar.

After reoperation for mechanical reasons (n=64), four additional patients developed joint sepsis, three in the one dose group and one in the three dose group. These cases of joint sepsis were omitted from analysis, because reoperation was defined as an end-point in the study.

Table III Joint sepsis wound healing, distant infections (hip replacements)

	one dose n=1327 (%)	three doses n=1324 (%)	p value x^2-test
joint sepsis (cat I)	11 (0 8)	6 (0 5)	0 17#
some signs of possible sepsis (cat II)	7 (0 5)	9 (0 7)	0 37##
postoperative wound infection	25 (1 9)	31 (2 3)	0 50
minor woundhealing disturbances	169 (12 7)	166 (12 5)	0 89
haematoma light	127 (9 6)	145 (11 0)	0 09
moderate	99 (7 5)	82 (6 2)	
severe	28 (2 1)	44 (3 2)	
any wound drainage	166 (12 5)	178 (13 4)	0 51
postoperative distant infections			
urinary tract	201 (15 2)	194 (14 7)	0 72
pulmonary tract	18 (1 4)	20 (1 5)	0 88
skin	31 (2 3)	26 (2 0)	0 59
septicaemia	5 (0 4)	4 (0 3)	0 99

(# = one-sided, ## = category I + II analysed together one-sided)

No significant differences were found between the groups with respect to postoperative wound infection, minor woundhealing problems, haematoma and wound drainage, the amount of additional antibiotics prescribed for wound problems and temperature e causa ignota (Table III).

Distant infections were not influenced by the method of prophylaxis (Table III). Most postoperative distant infections occurred in the urinary tract. In nine patients, septicaemia was documented during hospital admission, but only one patient developed subsequently joint sepsis. The amount of additional antibiotics prescribed for distant infections in both prophylaxis groups did not differ significantly (Table IV).

Table IV Additional postoperative antibiotics usage expressed in DDD# with number of replacements (n)

indication	one dose (n=1327) DDD	n	(%) ##	three doses (n=1324) DDD	n	(%) ##	p value x^2-test
wound infection	1241	48	(3.6)	1281	40	(3.0)	0.45
temperature e.c.i	416	18	(1.4)	356	18	(1.4)	1.00
distant infection	2040	196	(14.8)	2072	198	(15.0)	0.94
other reasons	164	35	(2.6)	57	24	(1.8)	0.15

(# = Defined Daily Doses, ## = % of replacements)

The number of (non)orthopaedic complications was well-matched between the groups (Table V). The number of invasive diagnostic procedures, such as gastroscopy, cystoscopy as well as operations performed for general complications, was slightly higher in the one dose group. There was no difference between the number of patients who died in the hospital. During follow-up, the number of patients who died due to cardio-respiratory disease was higher in the one dose group, but no relation with sepsis could be found.
Only five of the patients in our study group (0.2%) suffered allergic reactions associated with cefuroxime of which two were withdrawn from the analysis because they did not receive the full three doses. Anaphylactic shock was not registered.

Table V Complications, adverse effects and mortality (hip replacements)

		one dose n (%)	three doses n (%)	p value x^2-test
orthopaedic complications		48 (3.6)	46 (3.5)	0.92
orthopaedic reoperation (also in f-up)		33 (2.5)	31 (2.3)	0.91
non-orthopaedic complications		47 (3.5)	45 (3.4)	0.92
non-orthopaedic operations		18 (1.4)	7 (0.5)	0.046
invasive diagnostic procedures		12 (0.9)	5 (0.4)	0.15
adverse reactions cefuroxime		1 (0.1)	2 (0.2)#	0.99
died in hospital		11 (0.8)##	5 (0.4)##	0.21
died during follow-up	< 1 year	43 (3.2)	30 (2.3)	0.20
	> 1 year	18 (1.4)	13 (1.0)	

(# = two additional patients in the three dose group suffered from adverse reactions [withdrawn from analysis]. ## = four additional patients in the one dose group and eight in the three dose group died within 7 days [withdrawn from analysis - Table I])

Discussion

A low number of high risk patients were included in this series due to limited entry and exclusion because the use of gentamicin-impregnated bone cement. The follow-up was also relatively short and both factors may have influenced the sepsis rate, which was much lower than the expected 1%. Nevertheless, our overall incidence of 0.64% compares well with the 0.84% and 0.7% joint sepsis reported by Lidwell[4] and Hill[3] in patients operated in conventionally-ventilated operating theatres receiving prophylactic antibiotics.

The incidence of joint sepsis in the single dose group was almost double that in the three dose group (0.83 versus 0.45%); the numbers were small and the difference was not significant ($p > 0.05$). However, this negative chi-square test did not prove that the treatments were equally effective, since the confidence limits were so wide as that they included the possibility of large underlying differences.
The one-sided 95% confidence limits of the difference between the single dose group and the control group had a range of up to 0.9% and a ratio up 4.2 . Thus ultimately a more than doubled incidence could occur in the one dose group. This was, by the criteria set before the trial started, defined as unacceptable. The equal efficacy of the single dose of cefuroxime compared with three doses could therefore not be confirmed. Our trial sample with a low incidence of joint sepsis, was too small to draw definite conclusions. An extended follow-up, with probably more low grade infections diagnosed[16], may provide more conclusive data. We are now planning a 3-year follow-up evaluation.

The data on woundhealing problems were comparable with other reported series[3,17,18] although the definitions varied to some extent. In this study, the incidence of postoperative minor woundhealing problems, wound drainage and wound infection as well as the amount of antibiotic prescribed for wound problems and temperature e causa ignota, was not influenced by one dose or three doses of antibiotic prophylaxis.

The urinary tract was the most frequent site of distant infection and the 15% incidence was somewhat higher than the 4-9% reported in other studies[3,17,18]. This may be related to the large proportion of patients who received an urinary catheter postoperatively[19]. In one study, in which a 5-day regimen was compared to a placebo, the incidence of urinary tract infection was reported to be 5.8 and 9.9%, respectively[3]. In our series, no difference in the incidence of various postoperative distant

infections was found between the single and triple dose regimen. The amount of additional antibiotics prescribed for distant infections and other reasons was also similar in both groups. Adverse events associated with of cefuroxime were reported in only five patients (0.2%).

We were unable to confirm that the efficacy of a single perioperative dose of cefuroxime was equal to that of a three dose regimen, since there remains a considerable possibility that more than twice the incidence of sepsis could occur when more operations are performed The numbers of joint sepsis were too small to draw definite conclusions. A three dose regimen of cefuroxime is therefore recommended in hip replacement surgery until further data become available from an extended follow-up.

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References

1 Fogelberg E V, Zitzmann E K, Stinchfield F E, Prophylactic penicillin in orthopaedic surgery *J Bone and Joint Surg 52A* 95-98, 1970
2 Ericsson C E, Lidgren L, Lindberg L, Cloxacillin in the prophylaxis of postoperative infections of the hip *J Bone and Joint Surg 55A* 808-813, 1973
3 Hill C, Mazas F, Flamant R, Evrard J, Prophylactic cefazolin versus placebo in total hip replacement *Lancet I* 795-797, 1981
4 Lidwell O M, Lowbury E J L, Whyte W, Blowers R, Stanley S J, Lowe D, Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement A randomized study *Br Med J 2* 10-14, 1982
5 Pollard J P, Hughes S P F, Scott J E, Evans M J, Benson M K D, Antibiotic prophylaxis in total hip replacement *Br Med J 1* 707-709, 1979
6 Heydemann J S, Nelson C L, Short-term preventive antibiotics *Clin Orthop 205* 184-187, 1986
7 Evrard J, Dovon F, Acar J F, Salord J C, Mazas F, Flamant R, Two-day cefamandole versus five-day cephazolin prophylaxis in 965 total hip replacements *Int Orthop 12* 69-73, 1988
8 Gatell J M, Garcia S, Lozano L, Soriano E, Ramon R, Garcia Sanmiguel J, Perioperative cefamandole against infections *J Bone and Joint Surg 69A* 1189-1193, 1987
9 Norden C W, Prevention of bone and joint infections *Am J Med 78 (suppl 6b)* 229-232, 1985
10 Hirschmann J V, Antibiotics in the prevention of infection associated with prosthetic devices In Sugarmann B S, Young E J, *Infections associated with prosthetic devices* CRC-Press, 270-277, 1984
11. Pollock A V, Surgical prophylaxis- The emerging picture *Lancet I* 225-230, 1988
12 DiPiro J, Cheung R, Bowden T, Mansberger J A, Single-dose systemic antibiotic prophylaxis of surgical wound infection *Am J Surg 152* 552-559, 1986

13. Sanderson P.J., The choice between prophylactic agents for orthopaedic surgery. *J. Hosp. Inf. 11(suppl.C)*: 57-67, 1988.
14. Mackuch R., Simon R., Sample size requirements for evaluating a conservative therapy. *Cancer Treat. Rep. 62*: 1037-40, 1978.
15. Anonymous. *Nordic Statistics on Medicines 1981-83. Part II.*Nordic Drug Index with Classification and Defined Daily Doses. Uppsala: Nordic Council on Medicines 1985.
16. Lidwell O.M., Lowbury E.J.L., Whyte W., Blowers R., Stanley S.J., Lowe D., Extended follow-up of patients suspected of having joint sepsis after total joint replacement. *J. Hyg. Camb. 95*: 655-664, 1985.
17. Lidwell O.M., Lowbury E.J.L., Whyte W., Blowers R., Stanley S.J., Lowe D., Infection and sepsis after operations for total hip or knee-joint replacement: influence of clean air, prophylactic antibiotics and other factors. *J. Hyg. Camb. 93*: 505-529, 1984.
18. Surin V.V., Sundholm K., Backman L., Infection after total hip replacement. *J. Bone and Joint Surg. 65B*:412-418, 1983.
19. Garibaldi R.A., Burke J.P., Britt M.R., Miller W.A., Smith C.B., Meatal Colonization and catheter-associated bacteriuria. *N. Engl. J. Med. 303*: 316, 1980.

Chapter IV

Joint sepsis after prophylaxis with one or three doses of cefuroxime in 362 knee replacements

A randomized controlled multicentre study

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Summary

The efficacy of infection prophylaxis in knee replacement using one perioperative dose of cefuroxime was evaluated in a randomized controlled multicentre study. A three dose cefuroxime regimen was used as a control. All the operations were performed in conventionally-ventilated operating theatres. From the 455 operations registered, 58 were excluded and 35 were withdrawn, leaving 362 operations (345 patients) for analysis, 175 in the one dose group and 187 in the control group.

There were no differences between the incidence of haematoma and minor postoperative woundhealing problems, but there were more wound infections in the three dose group. The incidence of urinary tract and other distant infections as well as the amount of additional antibiotics used after the prophylaxis were similar in both groups.

During a mean follow-up of 12 months, joint sepsis was diagnosed in 3 out of the 175 operations in the one dose group (1.7%, 95% confidence limits 0 09-3 33%) and in 6 out of the 187 operations in the control group (3.2%, 95% confidence limits 0.63-5.77%). This difference was not significant (one tailed chi-square test, $p > 0.05$). Confidence limits of the difference between the one dose group and the three dose group revealed that with many more operations performed, the incidence of joint sepsis in the one dose group may ultimately be 1.78% higher. The trial sample of the present study however, is too small to draw definitive conclusions about the efficacy of a single dose in large patient populations.

The mean incidence of joint sepsis in knee replacements (2.45%) was nearly four times higher than the incidence in hip replacements performed at the same hospitals and using the same infection prophylaxis. The use of gentamicin bone cement is recommended in high risk patients.

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Introduction

Joint sepsis in total knee arthroplasty remains a major clinical problem[1] and it is the second most common reason for failure[2]. Perioperative systemic antibiotics are very effective in reducing the incidence of joint sepsis[3] and a 24-hour prophylaxis regimen is currently advised in joint replacement surgery[4]. In the past decade, a trend towards further reduction to a single dose has been noted in orthopaedic surgery[5-7] as well as in other surgical fields[8,9].

In order to establish the efficacy of a single perioperative dose for infection prophylaxis, a randomized controlled multicentre study was performed on hip and knee replacements[10]. The two operations could not be analyzed together, because the patient characteristics and the results of the knee replacements differed considerably from the hip replacements.

The purpose of this chapter is to report on a separate analysis of the knee replacements in relation to the incidence of joint sepsis, wound-healing problems and distant infections, after the application of infection prophylaxis using one dose or three doses of cefuroxime.

Patients and methods

The study population in this trial comprised the total knee replacements performed at twenty-two hospitals in the period from 1 July 1986 to 1 July 1988. Only hospitals with conventionally-ventilated operating theatres were invited to participate; the local ethics committees approved the protocol. Before the trial started, the assumed incidence of joint sepsis was 1% and the detectable difference was set at 1%[10]. An increased incidence of joint sepsis of less than 1% in the one dose group (which is less than twice the incidence found in the three dose group) was considered to be acceptable. As knee replacements are performed fairly infrequently, the number of replacements in this separate analysis was too small to meet the statistical requirements for the evaluation of conservative therapy[11].

Patients who underwent total knee arthroplasty were eligible for inclusion in the study. The exclusion criteria were cephalosporin allergy, penicillin anaphylaxis, the use of antibiotics less than forty-eight hours before operation, the use of perioperative antibiotics other than cefuroxime, malignancy in the operated joint, former or current sepsis in the joint and the use of gentamicin-impregnated bone cement for fixation of the prosthesis components. In one patient, tuberculous joint sepsis was

diagnosed. She was excluded retrospectively, because she had acquired this joint infection before the operation.

Randomization of the prophylaxis regimen was performed with a computerized list in blocks of ten numbers. For every eligible patient, an envelope was opened sequentially. From the envelope a self-adhesive label with the prescribed dosage on it was entered on the patient's records and anaesthesia records. Thus the treatment was not blinded. For logistic reasons, a number of centres randomized all the patients and exclusions were performed after the operation.

Cefuroxime is a second generation cefalosporine which provides a broad spectrum of activity against the organisms which cause joint sepsis in orthopaedic implants[12]. Both prophylaxis groups received an intravenous injection of 1500 mg cefuroxime at the induction of anaesthesia, thirty minutes before the incision and at least 20 minutes before the inflation of the tourniquet. This ensured adequate bone and soft tissue concentrations throughout the operation[13]. In the three dose group, a second and third dose of 750 mg cefuroxime was administered intravenously after 8 and 16 hours, respectively. Three centres rinsed the wound with a fluid containing an antibiotic and two centres used povidone iodine.

Definitions

The clinical end point of the study was joint sepsis, reoperation or death.

- Confirmed joint sepsis was defined as a positive culture at reoperation or a draining sinus. Strong evidence of sepsis was defined as four or more 'possible signs of infection'. These two groups were analysed together (category I).
- In patients who only showed two or three possible signs of sepsis (category II) a definite diagnosis could not be made. Patients with one or no signs (category III) were not suspected of having joint sepsis.

The conditions which were defined as being possible signs of infection at follow-up were: pain during weight-bearing and/or at rest, tenderness of the wound, fever, an abnormal X-ray (periostial reactions, progressive bone resorption), an increased ESR (20 mm above the preoperative value or > 35 mm), positive culture in the joint fluid aspiration, a positive arthrogram, a bone scan showing the typical signs of infection or an increased CRP.

- Wound infection in the postoperative period, was defined as erythema more than one centimetre from the incision.
- Minor postoperative woundhealing problems were defined as erythema of the wound less than one centimetre from the incision, pus suture, small wound dehiscence, necrosis of the wound edge and blisters.

- Distant infections were usually diagnosed on the basis of positive cultures. A urinary tract infection was defined as bacteriuria of more than 10^5 bacteria/ml. Blood cultures of *Staphylococcus epidermidis* were only considered positive when cultured at least twice. A few lung, skin and other infections were diagnosed on a clinical basis.

Additional antibiotics prescribed after the perioperative period for wound and/or distant infections or other reasons, were also recorded. The amount of antibiotic was expressed in Defined Daily Doses, which is based on the main indication and expressed as the weight of active substance[17].

The primary variable in the statistical analysis was joint sepsis (category I). Confidence limits (one-sided) were calculated for the difference and for the ratio of the crude rates in both groups. Other outcome variables were compared by using the chi-square test (two-sided) with a continuity correction.

Results

From 1 July 1986 to 1 July 1988, 455 operations were registered (Table I). On the basis of the criteria laid down in the protocol, 58 operations were excluded, the main reason being the use of gentamicin bone cement. From the remaining 397 knee replacements, 35 were withdrawn owing to protocol deviations, leaving 362 replacements (345 patients) for analysis.
A separate follow-up (not included in the analysis) was performed on all the withdrawn patients. One patient in the one dose group had developed joint sepsis (Table III) and was also found to have received an incorrect dose.
At many of the hospitals, knee replacement, unlike hip replacement, was not a routine procedure. Nine hospitals contributed less than 10 replacements to the trial and only eight contributed more than 20. The mean follow-up period was twelve months in both groups. None of the patients were lost to follow-up.

Table I Entrance criteria, exclusions and withdrawals (knee replacements)

	Number of operations		
	one dose	three doses	total
RANDOMIZED	246	259	505
OPERATIONS registered #	225	230	455
EXCLUSIONS protocol	33 (14 7%)	25 (10 9%)	58 (12 7%)
FOLLOW-UP	192	205	397
WITHDRAWN FROM ANALYSIS	17 (8 9%)	18 (8 8%)	35 (8 8%)
other type of antibiotic	4	1	5
died within 7 days	-	-	-
wrong dose or administration	11	13	24
second replacement ##	2	4	6
SUITABLE FOR ANALYSIS	175	187	362

(# = in some patients, the operation was cancelled or a different procedure was performed, ## = during one hospital admission)

The general and orthopaedic characteristics (Table II) of the prophylaxis groups were well-matched, except for the increased incidence of cardiac disease in the three dose group. The number of previous operations was also slightly increased in the three dose group. The peroperative data were well-matched in both trial arms.

Table II General and orthopaedic characteristics (knee replacements)

	one dose n=175	three doses n=187
mean age yr (SD)	70 6 (9 6)	71 1 (9 3)
sex - male/female	23/152	23/164
operated side - left/right	80/95	89/98
mean quetelet index (SD)	27 2 kg/m^2 (4 5)	27 4 kg/m^2 (4 5)
physical condition (moderate)	36	39
steroid use	17	17
diabetic #	9	8
cardiac disease #	9	24
pulmonary disease #	6	6
preoperative infections	16	23
no other concurrent illness #	95	95
DIAGNOSIS		
osteoarthritis	101	89
rheumatoid arthritis	41	51
prosthesis failure	2	5
other previous operations	31	42

Table II continued

	one dose n=175	three doses n=187
TYPE OF REPLACEMENT		
bone cement used	133	141
non-constrained prosthesis##	145	148
status of surgeon staff/resident	167/8	177/10
mean blood loss (SD)[mv]	361(310)[89]	322(248)[79]
mean operation time (SD)[mv]	105(26)[3]	107(29)[-]
breakdown of sterility (> 90% hole in glove)	5	10

((SD) = standard deviation, [mv] = number of missing values, # = more than one concurrent illness per patient possible, ## = majority of other prosthesis were semiconstrained except one constrained prosthesis in each group)

No significant differences were found between the two prophylaxis groups with respect to haematoma, minor woundhealing problems, wound drainage and the amount of antibiotics (in DDD) prescribed for wound problems and temperature e.c.i. (Table III). The incidence of wound infections was higher in the three dose group, but the numbers were very small (9 versus 4).

Joint sepsis was diagnosed in three patients in the one dose group (1.71%, 95% confidence limits 0.09-3.33%) and in six patients in the three dose group (3.20%, 95% confidence limits 0.63-5.77%). The estimated difference between the incidence of joint sepsis in the one dose group minus the three dose group was -1.49% (95% upper confidence limit 1.78%). The estimated ratio was 0.53 with an 95% upper confidence limit of 1.69.

Joint sepsis was confirmed by a positive culture at reoperation and/or a draining sinus in eight patients; in the remaining patient, there was strong evidence of joint sepsis. Joint sepsis was diagnosed in three cases within one month, in three more cases after three months, in one case after four months, in one after five months and a further one after ten months.

Six of the nine patients with joint sepsis were also found to be suffering from rheumatoid arthritis: two in the one dose group and four in the three dose group. There were two joint sepsis-related deaths, one in each prophylaxis group; both were suffering from rheumatoid arthritis. The final outcome in three other patients with joint sepsis was arthrodesis, resection arthroplasty and amputation, respectively. In two cases, reimplantation was performed.

Three out of the 26 patients who underwent 'mechanical' reoperation subsequently developed joint sepsis. They were not included in the analysis because reoperation was defined as an end-point in the study.

Table III Joint sepsis, woundhealing, distant infection (knee replacements)

	one dose n (%)	three doses n (%)	p-value x^2-test
joint sepsis (cat. I)	3 (1.7)$	6 (3.2)	0.89 #
signs of possible sepsis (cat. II)	1 (0.6)	5 (2.7)	0.98 ##
postoperative wound infection	4 (2.3)	9 (4.8)	0.31
minor woundhealing disturbances	33 (18.9)	35 (18.7)	0.92
any wound drainage	30 (17.1)	38 (20.3)	0.52
haematoma: slight	19 (10.9)	13 (7.0)	0.47
moderate	23 (13.1)	26 (13.9)	
severe	5 (2.9)	9 (4.8)	
postoperative distant infections:			
urinary tract	32 (18.3)	34 (18.8)	0.91
pulmonary tract	3 (1.7)	4 (2.1)	0.79
other	2 (1.1)	1 (0.5)	0.95
septicaemia	- -	2 (1.1)	0.51

($ = one withdrawn patient in the one dose group developed joint sepsis,
= one-sided, ## = category I + II analysed together one-sided)

The incidence of distant infections was not influenced by the one dose or three dose regimen (Table III). Most distant infections occurred in the urinary tract. There were two patients with documented septicaemia (positive blood culture). The amount of antibiotics (in DDD) prescribed for distant infections and other reasons in both treatment groups did not differ (Table IV).

Table IV Amount of additional postoperative antibiotics used (expressed in DDD# with number of knee replacements (n))

indication	one dose (n=175) DDD	n	(%)##	three doses (n=187) DDD	n	(%)##	p value x^2-test
wound	387	11	(6.3)	389	15	(8.0)	0.66
temperature eci	99	8	(4.6)	140	7	(3.7)	0.90
distant infection	382	30	(17.1)	355	38	(20.3)	0.52
other reasons	6	7	(4.0)	6	5	(2.7)	0.94

(# = Defined Daily Doses, ## = percentage of knee replacements)

There was no difference in the number of orthopaedic and non-orthopaedic complications between the groups (Table V). In the three

dose group, the number of orthopaedic reoperations more than doubled that in the one dose group. This was mainly due to reoperations performed for patellofemoral problems, without any relation to sepsis. The incidence of adverse events associated with cefuroxime was low (0.5%).

Table V Complications, adverse effects and mortality

	one dose n (%)	three doses n (%)	p value x^2-test
orthopaedic complications	4 (2.3)	5 (2.7)	0.92
orthopaedic reoperation (also f-up)	8 (4.6)	18 (9.6)	0.097
non-orthopaedic complications	6 (3.4)	5 (2.7)	0.91
non-orthopaedic operations	3 (1.7)	5 (2.7)	0.79
adverse events cefuroxime#	2 (1.1)	-	-
death in hospital	1 (0.6)	-	0.69
death during follow-up	5 (2.9)	9 (3.2)	

(# = no anaphylactic shock was registered)

Discussion

In this series of total knee replacements, the number of high risk patients was reduced due to their limited entry and the exclusion criterion regarding the use of gentamicin bone cement. These factors in addition to the relatively short period of follow-up, may have reduced the sepsis rate in the trial. The fact that knee replacement, unlike hip replacement, was not a routine procedure at several hospitals, may also have influenced the incidence.

The overall incidence in this trial of 2.45% is well-matched with the incidences mentioned in other series, which vary from a minimum of 1.3% up to a maximum of 4.4% using systemic antibiotics and, in the majority of cases, a two or three compartmental prostheses[1,2,15-18].

The incidence of joint sepsis in the three dose group was double that in the one dose group, as was the number of wound infections. This difference was most unexpected, because more antibiotics were given in the three dose group and the groups were reasonably well-balanced with respect to patient characteristics (Table II). The difference between the treatment groups was not statistically significant ($p > 0.05$). This did not prove that the treatments were equally effective, since the confidence limits were so wide that they included the possibility of large underlying differences, from very low percentages to an extreme of more than 5% in the three dose group. The confidence limits of the difference between the one dose and the three dose group showed that an even higher inci-

dence (max. 1.78% more joint sepsis) may be possible in the one dose group with more operations performed. These wide margins indicate that the number of patients is too small to be able to draw definitive conclusions regarding the efficacy of a one dose regimen of cefuroxime.

Apart from joint sepsis and postoperative wound infection, no differences were found between the one dose and three dose group with respect to minor woundhealing problems, wound drainage, haematoma and the amount of antibiotics (in DDD) prescribed for wound problems. The overall incidence of woundhealing problems was high, but lay within the range of 5-25% reported in other series[15,17,19,20]. Perioperative wound rinsing with povidone iodine or a fluid containing an antibiotic, did not influence the incidence of joint sepsis.

We did not find any difference between the two prophylaxis groups regarding the incidence of urinary tract and other postoperative distant infections, nor in the amount of antibiotics (in DDD) used to treat these infections. It is not likely that a short course of perioperative antibiotics would exert any influence on urinary tract infections. The incidence is probably more determined by the rate and duration of catheterization[21,22].

Bearing in mind that all the total knee replacements and hip replacements were operated on by the same surgeons, using the same prophylaxis regimen, at the same hospitals, it is quite remarkable that there was such a difference between the incidence of joint sepsis (2.45% and 0.65%, respectively)[10]. Rheumatoid arthritis may have been partly responsible for this difference, as it has proved to be an important risk factor for joint sepsis in other series[1,2,16-18,23]. In this series of total knee replacements, 6 out of the 107 patients with rheumatoid arthritis developed joint sepsis (5.9%), whereas only 3 out of the 255 (1.18%) without rheumatoid arthritis developed joint sepsis[24].
In order to find methods for reducing the higher incidence of joint sepsis in knee replacements performed in conventionally-ventilated operating theatres, trials with additional prophylactic measures, such as gentamicin bone cement[25], should be performed on patients undergoing cemented knee replacement. The routine use of gentamicin bone cement is certainly recommended in patients with rheumatoid arthritis and/or other risk factors.

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References

1. Rand J.A., Fitzgerald R.H.. Diagnosis and management of the infected total knee arthroplasty. *Orthop Clin. North. Am. 20*: 201-210, 1989.
2. Knutson K., Lindstrand A., Lidgren L., Survival of knee arthroplasties. A nation-wide multicenter investigation of 8000 cases. *J. Bone and Joint Surg 68B*: 795-803, 1986.
3. Lidwell O.M., Lowbury E.J.L., Whyte W., Blowers R., Stanley S.J., Lowe D., Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement: A randomized study. *Br. Med. J. 2*: 10 -14, 1982.
4. Norden C.W., Prevention of bone and joint infections. *Am. J. Med. 78 (suppl 6b)*: 229-232, 1985.
5. Heydemann J.S., Nelson C.L., Short-term preventive antibiotics. *Clin. Orthop. 205*: 184-187, 1986.
6. Gatell J.M., Garcia S., Lozano L., Soriano E., Ramon R.,Garcia Sanmiguel J., Perioperative cefamandole against infections. *J. Bone and Joint Surg. 69A*: 1189-1193, 1987.
7. Hirschmann J.V., Antibiotics in the prevention of infection associated with prosthetic devices. In: Sugarmann B.S., Young E.J., *Infections associated with prosthetic devices*. CRC-Press, 270-277, 1984.
8. Pollock A.V., Surgical prophylaxis-The emerging picture. *Lancet I*: 225-230, 1988.
9. DiPiro J., Cheung R., Bowden T., Mansberger J.A., Single-dose systemic antibiotic prophylaxis of surgical wound infection. *Am. J. Surg.152*: 552-559, 1986.
10. Wymenga A.B., Van Horn J.R., Theeuwes A., Muytjens H.L., Slooff T.J.J.H., Joint sepsis after infection prophylaxis with one or three doses of cefuroxime in 2631 hip replacements. A randomized controlled multicentre trial. Submitted for publication.
11. Mackuch R., Simon R., Sample size requirements for evaluating a conservative therapy. *Cancer Treat. Rep. 62*: 1037-1040, 1978.
12. Sanderson P.J., The choice between prophylactic agents for orthopaedic surgery. *J. Hosp. Inf. 11(suppl.C)*: 57-67, 1988.
13. Johnson D.P., Antibiotic prophylaxis with cefuroxime in arthroplasty of the knee. *J. Bone and Joint Surg. 69B*: 787-789, 1987.
14. Anonymous. *Nordic Statistics on Medicines 1981-83. Part II.* Nordic Drug Index with Classification and Defined Daily Doses. Uppsala: Nordic Council on Medicines 1985.
15. Insall J., Scott W.N., Ranawat C.S., The total condylar knee prosthesis. *J. Bone and Joint Surg. 61A*: 173-180, 1979.
16. Grogan T.J., Dorey F., Rollins J., Amstutz H.C., Deep sepsis following total knee arthroplasty. *J. Bone and Joint Surg. 68A*: 226-234, 1986.
17. Johnson D.P., Bannister G.C., The outcome of infected arthroplasty of the knee. *J. Bone and Joint Surg. 68B*: 289-291, 1986.
18. Bengtson S., Knutson K., Lidgren L., Treatment of infected knee arthroplasty. *Clin. Orthop. 245*: 173-178, 1986.
19. Jones E.C., Insall J.N., Inglis A.E., Ranawat C.S., Guepar knee arthroplasty results and late complications. *Clin. Orthop. 140*:145-152, 1979.
20. Kaufer H., Matthews L.S., Spherocentric arthroplasty of the knee. *J. Bone and Joint Surg. 63A*: 545-559, 1981.
21. Garibaldi R.A., Burke J.P., Britt M.R., Miller W.A., Smith C.B., Meatal Colonization and catheter-associated bacteriuria. *N. Engl. J. Med. 303*: 316, 1980.
22. Wymenga A.B., Muytjens H.L., van Horn J.R., Theeuwes A., Slooff T.J.J.H., The relation wound, urine cultures and joint sepsis after hip and knee replacement. Submitted for publication.

23. Lidwell O.M., Lowbury E.J.L., Whyte W., Blowers R., Stanley S.J., Lowe D., Infection and sepsis after operations for total hip or knee-joint replacement: influence of clean air, prophylactic antibiotics and other factors. *J. Hyg. Camb. 93*: 505-529, 1984.
24. Wymenga A.B., Muytjens H.L., Van Horn J.R., Theeuwes A., Slooff T.J.J.H., Risk factors for joint sepsis in knee replacement. An analysis of 362 knee replacements. Submitted for publication.
25. Josefsson G., Lindberg L., Wiklander B., Systemic antibiotics versus gentamicin-containing bone cement in the prophylaxis of postoperative infection in total hip arthroplasty. *Clin. Orthop. 159*: 194-200, 1981.

Chapter V

Risk factors for joint sepsis in hip replacement

An analysis of 2651 operations

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Summary

Risk factors associated with joint sepsis were investigated in 2547 patients with 2651 hip replacements who were examined in a prospective multicentre trial. The operations were performed in the period from 1 July 1986 to 1 July 1988 at 27 hospitals with conventionally-ventilated operating theatres. All the patients received a short course of perioperative cefuroxime. After a mean follow-up of 13 months, joint sepsis was diagnosed in 17 patients(0.64%).

The following factors were found to be associated with an increased risk ratio (RR) for joint sepsis: diabetes(RR=3.7), failed fracture osteosynthesis(RR=5.4), a breakdown of sterility(RR=3.4) and surgical reintervention (RR=9.5).

Patients who suffered from wound infection after the operation ran a very high risk of developing joint sepsis (RR=62.2). In patients for whom it was indicated to perform wound or blood cultures, it was 11.6 and 7.3 times as high as in patients without these signs and symptoms, respectively. In patients with a urinary tract infection, the risk was 4.9 times increased. Risk factors at discharge from hospital were an unhealed wound (RR=22.2) and a slow reconvalescence period (RR=5.2).

The use of gentamicin bone cement as an additional prophylactic measure might reduce the incidence of joint sepsis in high risk patients and its application is therefore recommended in these patients. Patients with diabetes should be carefully prepared and monitored during the period of hospitalization.

If patients develop a wound infection, adequate antibiotic therapy should be instigated, with its course guided by the wound culture results. Minor woundhealing problems do not form an indication for antibiotic treatment. In patients with a wound infection and a draining haematoma, surgical evacuation might salvage the joint as we found in 3 out of our 4 patients. Patients who are discharged from hospital with an unhealed wound or a slow rate of reconvalescence, should receive adjunctive follow-up care.

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Introduction

Joint sepsis after hip replacement is a devastating complication. The incidence is related to environmental factors, such as air contamination and the use of perioperative antibiotics[6,12,16] From the data obtained during a large multicentre study, Lidwell et al.[11] calculated that in conventionally-ventilated operating theatres, approximately 90-95% of the cases of joint sepsis were initiated during the operation. The application of perioperative antibiotics has been reported to achieve a four to six-fold reduction in the incidence of joint sepsis[6,11,23].

Besides environmental factors, individual patient characteristics also play an important role in the development of joint sepsis. For example, the preoperative medical and orthopaedic diagnoses, characteristics of the operative procedure and postoperative events all demonstrate a relationship with joint sepsis. The importance of any particular risk factor may vary at the various levels of joint sepsis.

The purpose of this study was to investigate the risk factors which are associated with joint sepsis in 2651 hip replacements in 2547 patients, all operated on in conventionally-ventilated operating theatres, with a short course of perioperative antibiotic prophylaxis.

Patients and methods

From July 1986 to July 1988, a prospective randomized controlled trial was performed at 27 hospitals with conventionally-ventilated operating theatres, in order to investigate the efficacy of one dose of cefuroxime (1500 mg i.v. at the induction of anaesthesia) in hip replacement. Patients receiving a three dose cefuroxime regimen (perioperative dose 1500 mg, subsequent doses of 750 mg i.v. after 8 and 16 hrs., respectively) served as a control.

A relevant summary is given in this section, as details were reported elsewhere[26]. A total of 3074 hip replacements were eligible for entry into the trial, of which 278 were excluded. The most frequent reason for exclusion was the use of gentamicin-impregnated bone cement, which was used in high risk patients. This series therefore represents a rather homogeneous group of patients who underwent hip replacement procedures, as a number of high risk patients were excluded. Further important exclusion criteria were the use of other antibiotics and former or current sepsis in the joint.

From the remaining 2796 hip replacements, 145 were withdrawn for the following reasons: the wrong type and/or dose of antibiotics had been administered, the patient died (not sepsis-related) within 7 days of

the operation or a second replacement had to be performed during the same period of hospitalization. This left 2651 hip replacements (2547 patients) for analysis.
In the analysis, the end point of participation in the follow-up was defined as reoperation or death, but a separate analysis was done on the reoperations (performed for mechanical reasons). The mean follow-up was 13 months. In the one dose group (n=1327), 11 patients suffered from joint sepsis (0.83%, 95% confidence limits 0.33-1.32) and in the three dose group, 6 patients (0.45%, 95% confidence limits 0.08-0.81). The estimated difference between the one dose group and the three dose group was 0.38% (95% confidence limits 0-0.9%). Therefore, we could not confirm that one dose of cefuroxime has the same prophylactic efficacy as a three dose regimen in hip replacement. A longer follow-up, which will probably lead to more diagnoses of joint sepsis, is needed to provide more conclusive data[26].

Definitions

- Confirmed joint sepsis was defined as a positive culture at reoperation or a draining sinus.
- Strong evidence of joint sepsis was defined as four or more possible signs of sepsis (pain during weight-bearing and/or at rest, tenderness of the wound, fever, an abnormal X-ray with periostial reactions, progressive bone resorption, an increased ESR (20 mm above the preoperative value or > 35 mm), a positive culture in the joint fluid aspiration, a positive arthrogram, a bone scan showing the typical signs of infection or an increased C-reactive protein.

- Wound infection in the postoperative period, was simply defined as erythema of the wound more than one centimetre from the incision.
- Minor postoperative woundhealing problems were defined as erythema of the wound lesss than one centimetre from the incision, pus suture, small wound dehiscence, necrosis of the wound edge and blisters.

- Distant infections were usually diagnosed on the basis of positive cultures.Urine cultures were considered positive if bacteriuria was present with more than 10^5 bacteria per ml. A few lung, skin and other infections were also diagnosed on a clinical basis.

Statistical analysis

Joint sepsis rates within subgroups were estimated as crude rates. Univariate analysis of all the potential risk factors was performed with the chi-square test. From all the risk factors tested, only those with a p-value of $p <= 0.1$ were considered significant. These, and a few other interesting risk factors, are summarized in Tables 1a-d.
The number of times the risk for joint sepsis is increased, can be expressed as the risk ratio (RR).

$$\text{RISK RATIO} = \frac{\%\,\text{JOINT SEPSIS WITH RISK FACTOR}}{\%\,\text{JOINT SEPSIS WITHOUT RISK FACTOR}}$$

As it is possible for risk factors to be related to each other, their importance can be overestimated in a univariate analysis. To overcome this problem, a multiple logistic regression analysis was carried out. This method identifies the risk factors whose influence is independent of any other simultaneously occurring risk factor(s). In this way we identified separate risk factors which have an additive effect on the risk of joint sepsis, i.e. the more factors a patient has, the higher the risk of joint sepsis.
Four separate groups of risk factors were analysed: perioperative factors (1a), postoperative factors (1b), cultures (1c) and risk factors at discharge from hospital (1d). Within each section, a regression analysis was performed (Tables IIa-d).

Results

Joint sepsis

Confirmed joint sepsis was diagnosed in fourteen patients. Three patients had strong evidence of joint sepsis, of whom two underwent reoperation for joint sepsis, but demonstrated negative cultures despite the clinical evidence. From the third patients, the joint aspirate grew *Staphylococcus aureus.*

Preoperative and perioperative risk factors (Table Ia)

In the univariate analysis, the following preoperative risk factors were not found to be associated ($p > 0.1$) with joint sepsis: sex, age, the cefuroxime dose (one dose or three doses), the quetelet index (kg/m^2),

physical condition, number of days in hospital before the operation, preoperative infections of the urinary tract, lung or skin, a urine sediment with more than 5 leucocytes per field (400x), the use of steroids and the orthopaedic diagnosis.
Patients with diabetes had an increased risk for joint sepsis. Patients who had previous surgery were also at risk. One revision of a failed cup arthroplasty out of 66 revisions became infected and for patients with failed fracture osteosynthesis the risk was even higher. In the group with other previous procedures (80% being osteotomies) no joint sepsis was diagnosed.

From the perioperative risk factors, the surgical approach (lateral or posterolateral), the use of bone cement versus fixation without cement, the degree of difficulty of the operation, the operation time, the amount of blood loss and the status of the surgeon (staff or resident), did not display a significant relationship with joint sepsis. The results of routine cultures of the joint, sampled during the operation at several hospitals, were not related to joint sepsis either.
During 6% of the operations, a breakdown of sterility occurred. In more than 90% of the cases, this was caused by a hole in the inner surgical glove. Three patients (1.91%) in this group suffered from joint sepsis. During two operations, a glove ruptured and during another operation the close contact between the glove and the sleeve of the gown was lost. In one patient *Staphyloccus epidermidis* was cultured at reoperation, in two other patients joint cultures were not available.

Table Ia Univariate risk factor analysis: preoperative and perioperative data

Risk factor	n	Joint sepsis n (%)	risk ratio	p value #
diabetes	100	2 (2.00)	3.4	0.08
no diabetes	2551	15 (0.59)	-	
rheumatoid arthritis	168	1 (0 60)	1.0	0.52
fracture (fresh/old)	334	4 (1.20)	2.1	
other diagnosis	78	0 (0.00)	-	
arthrosis	2071	12 (0.58)	-	
prosthesis	66	1 (1.52)	2.6	0.05
fracture osteosynth.	63	2 (3.17)	5.5	
other	125	0 (0.00)	0	
no previous surgery	2397	14 (0.58)	-	
break in sterility	157	3 (1.91)	3.4	0.04
complete sterility	2494	14 (0.56)	-	

(# = chi-square test, $p <= 0.1$ is significant)

Further analysis of the most important preoperative and perioperative risk factors derived from the multiple logistic regression analysis, showed that diabetes, failed fracture treatment and a breakdown of sterility, each acted as a separate risk factor for joint sepsis (Table IIa). This was validated by the observation that 6 out of the 291 patients with one or more of these three factors developed joint sepsis (1.9%), versus 11 out of the 2343 patients who did not display these factors (0.5%).

Postoperative woundhealing and other factors (Table Ib)

Univariate analysis showed that the presence of minor woundhealing problems, the day of vacuum-drain removal and the use of an indwelling urinary catheter, were not related to joint sepsis. Moreover, orthopaedic complications (n=94), such as nerve damage, dislocations and fractures which were treated conservatively, were not related to joint sepsis, nor were non-orthopaedic complications (n=88) which mainly occurred in the cardiovascular and gastrointestinal tract. Patients who underwent additional non-orthopaedic surgery on the urinary tract (n=7), the gastrointestinal tract (n=10), pacemaker implantation (n=3), skin necrotomy (n=4) and lower leg amputation (n=1) during the period of hospitalization, did not develop joint sepsis either.

Moderate and severe haematomas were clearly related to joint sepsis in univariate analysis. Patients with early postoperative wound drainage were also more at risk or joint sepsis. The risk for patients with serous drainage was 4.5 times higher and the risk for patients with blood or pus draining from the wound was even higher. Discharge from the orifice arising more than 24 hours after the removal of the drain occurred fairly often, but was less strongly related to joint sepsis. Postoperative wound infection was highly related to joint sepsis, 16% of these patients developed joint sepsis. Patients who had antibiotics prescribed for wound problems were also very much at risk for joint sepsis.

The multiple logistic regression analysis of the postoperative data revealed that wound infection was the only factor which acted independently (estimated RR = 62.2, Table IIb). The other (univariate) risk factors for postoperative sepsis, such as wound drainage and antibiotics, were apparently only acting in association with wound infection.

Table Ib Univariate risk factor analysis postoperative woundhealing

Risk factor		Joint sepsis n	Joint sepsis n (%)	risk ratio	p value #
haematoma	light	272	1 (0 37)	0 7	0 03
	moderate	181	3 (1 66)	3 2	
	severe	72	2 (2 78)	5 3	
	none	2126	11 (0 52)	-	
wound drainage	serous	295	4 (1 36)	4 5	0 00
	blood	29	2 (6 90)	23 0	
	pus	20	4 (20 00)	66 6	
	none	2307	7 (0 30)	-	
discharge drain orifice		374	5 (1 34)	2 5	0 07
no discharge		2277	12 (0 53)	-	
wound infection present		56	9 (16 07)	51 8	0 00
no wound infection		2595	8 (0 31)	-	
antibiotics for wound		88	8 (9 76)	27 9	0 00
no antibiotics		2563	9 (0 35)	-	

(# = chi-square test, p < = 0 1 is significant)

Cultures of the wound and other sites (Table Ic)

The number of postoperative gastrointestinal and lung cultures performed was small (n=42) and there was no relationship with later joint sepsis. Patients in whom there was an indication for performing a postoperative wound culture, were clearly at risk for joint sepsis and the risk was higher for patients with a positive culture. Patients with positive vacuum-drain cultures were also more at risk.

The urinary tract was the most frequent site of distant postoperative infection (15%). Patients with this complication had an increased risk of developing joint sepsis. Patients with skin infections (mainly skin ulcers and decubital sores on the sacrum and calcaneus) were also more at risk for joint sepsis. In the four patients with joint sepsis and sores, the sores developed after the operation.

Patients in whom a blood culture was performed for elevated temperature and/or signs of infection, were at risk for joint sepsis. Nine patients had documented septicaemia (positive blood cultures) and one of them developed joint sepsis. She was not reoperated on and blood cultures could not be matched with the causative bacteria of joint sepsis.

The multiple logistic regression analysis (Table IIc) showed that wound cultures (positive or negative), positive postoperative urine cultures and blood cultures (either positive or negative) were risk factors which acted independently in relation to joint sepsis. Validation showed that in the patients with one or more of these factors (n=533), 14 (2.62%) suffered from joint sepsis, whereas there were only three cases (0.14%) in the patients without these factors (n=2118).

Table Ic Univariate risk factor analysis wound and other cultures

Risk factor			Joint sepsis n	(%)	risk ratio	p value #
wound culture	negative	50	1	(2 00)	4 5	0 00
	positive	77	5	(6 49)	14.8	
	not done	2524	11	(0 44)	-	
drain culture	negative	684	3	(0 44)	0 9	0 00
	positive	122	5	(4 10)	8 4	
	not done	1845	9	(0 49)	-	
urine culture·	negative	274	-	(0 00)	0 0	0 00
	positive	395	9	(2 28)	5 7	
	not done	1982	8	(0 40)	-	
skin infection	present	57	4	(7 02)	14 0	0 00
	no infection	2594	13	(0 50)	-	
blood culture	negative	72	3	(4 71)	9 2	0 00
	positive	9	1	(11 1)	21 8	
	not done	2570	13	(0 51)	-	

(# = chi-square test, p < = 0 1 is significant)

Situation at discharge from hospital (Table Id)

Patients with an unhealed wound or an elevated temperature at discharge from hospital were at risk for joint sepsis. A prolonged and difficult postoperative reconvalescence period during hospitalization and a painful and limited function of the hip joint were also significant risk factors.

Multiple logistic regression analysis revealed that an unhealed wound at discharge from hospital and a prolonged and difficult period of reconvalescence acted as two independent risk factors (Table IId). Validation showed that in the patients with one or more of these factors (n=206), 8 (3.9%) developed joint sepsis, versus 9 out of the 2445 patients (0.36%) without these factors.

Table Id Unwariate risk factor analysis: situation at discharge

Risk factor	n	Joint sepsis n	(%)	risk ratio	p value #
wound not healed	38	4	(10.53)	21.6	0.00
healed	2613	13	(0.50)	-	
temperature elevated	29	1	(3.45)	5.6	0.06
normal	2622	16	(0.61)	-	
function limited, pain	95	2	(2.11)	3.6	0.07
pain-free	2556	15	(0.59)	-	
reconvalescence slow	172	5	(2.91)	6.1	0.00
normal	2479	12	(0.48)	-	

(# = chi-square test, $p < = 0.1$ is significant)

Table II a-d Multivariate analysis of risk factors

	beta	SE	risk ratio #
a Diabetes	1.3	0.8	3.7
Failed fracture osteosynth.	1.7	0.8	5.4
Breakdown of sterility	1.2	0.6	3.4
b Wound infection	4.1	0.5	62.2
c Wound culture done	2.5	0.5	11.6
Postop. urine culture pos.	1.6	0.5	4.9
Blood culture done	2.0	0.6	7.3
d Wound not healed	3.1	0.6	22.2
Slow reconvalescence	1.8	0.6	5.2

(a = preoperative and peroperative risk factors, b = woundhealing problems, c = cultures, d = situation at discharge from hospital, beta = regression coefficient, SE = standard error, # = estimated risk ratio = e^{beta})

Mechanical reoperation

The patients who underwent mechanical reoperation were included in the analysis up to the time of reoperation. A separate follow-up was performed on this group after the surgery. The most frequent indications for reintervention were femoral loosening of a prosthesis which had been applied without cement, and dislocation. Four out of the 64 (6.3%) patients with these complications developed joint sepsis versus 17

out of 2587 without reintervention (0.7%, RR=9.5).
Two patients with joint sepsis after reoperation needed surgical intervention for an irreducible dislocation, one on the day of the index operation and one after three weeks. In one patient, a non-cemented femoral component used in a revision procedure, was revised after six months. In one patient, a segment ring was added to the acetabular cup for recurrent dislocations after seven months. All of these four patients developed early wound infection and joint sepsis after reintervention, despite the administration of perioperative antibiotics.

Discussion

A number of independently acting risk factors were identified in 2547 patients who underwent 2651 hip replacements in conventionally-ventilated operating theatres and received a short course of perioperative antibiotics.
Diabetes is a well-recognized risk factor[18], although it is not always found to influence the postoperative course of recovery[4]. The cellular immune system may be weakened by the disease[21]. Rheumatoid arthritis was not related to joint sepsis in this series, perhaps due to the limited numbers or the relatively short follow-up; Poss[19] found an increased sepsis rate in rheumatoid arthritis only after a longer follow-up. The increased susceptibility of patients with rheumatoid arthritis has been confirmed by others[1,4,13,22].
Patients with failed fracture osteosynthesis in addition to prosthesis failure were at risk for joint sepsis in this study. In many other studies[1,4,17,19,23], an increased risk was found after previous surgery, except in two large series[13,22]. Reintervention soon after the index operation is also known to be an important risk factor for joint sepsis[23].
The significance of increased joint sepsis in relation to a breakdown of sterility in this study is evident and it is logical to theorize that contamination with skin flora from the surgeon's hand may enhance joint sepsis. Especially the isolation of *S. epidermidis* from the joint of one of our patients supports this theory. McCue[15] found perforations in 15% of the inner gloves used in total hip replacements, but none of the gloves grew bacteria colonies. The size of the glove perforations in our study were probably fairly large, as they were discovered macroscopically, but the consequences of this on the extent of contamination is unknown.

In patients who are known to have risk factors preoperatively or perioperatively, such as diabetes, rheumatoid arthritis and previous surgery, the use of gentamicin bone cement is recommended, because there is

some evidence that the use of gentamicin bone cement in combination with systemic antibiotics reduces joint sepsis in high risk groups[8,14,24] Perhaps patients with a breakdown of sterility during the operation would also benefit. In patients who have undergone previous surgery, it is obvious that low-grade sepsis should always be excluded[4,19] using all the necessary diagnostic efforts, including culturing of multiple biopsies from periprosthetic tissue[5,9].

Postoperative wound infection (erythema of the wound more than one centimetre from the incision), was a very strong predictor of joint sepsis; this complication was often accompanied by haematoma and discharge from the wound. An attempt should be made to reduce the incidence of joint sepsis in these high risk patients[4,10] by early diagnosis and treatment with adequate antibiotics. Treating minor woundhealing problems with antibiotics is not recommended, because the risk of joint sepsis is low.
We agree with Fitzgerald[4] that in the case of wound infection in combination with a draining haematoma, surgical evacuation of the infected haematoma is indicated and the patient should be treated with additional antibiotics. This procedure salvaged three out of the four hip replacements with these complications in our series.
Antibiotic treatment should be guided by the results of the wound culture, because when joint sepsis is preceded by wound infection, the organisms isolated from the joint are the same as those isolated from the postoperative wound in the large majority of cases[13]. We found this in four out of six patients with joint sepsis.

Not all cases of joint sepsis are preceded by wound infection. In five out of the 17 patients with joint sepsis in this series, the postoperative wound healed uneventfully. Lidwell[13] et al. calculated that two-thirds of the cases of joint sepsis were not preceded by any indication of wound sepsis and Surin[23] et al. found that the wound had healed uneventfully in 18 out of the 34 patients with joint sepsis.

The patients with positive urinary tract cultures in this study were at risk for joint sepsis, as has also been reported in other series[4,23], although one other study did not find a significant relationship[6]. Usually no clear correlation can be found between the pathogens of urinary tract infections and hip joint sepsis, so a causal relationship cannot be established. There are, however, a number of case reports in which early postoperative haematogenous seeding from the urinary tract is documented[2,3,7,25]. We found only one patient with similar microorganisms in the urine postoperatively who later developed joint sepsis, but haematogenous

seeding did not occur until 5 months after surgery and not in the early postoperative period.

An unhealed wound at discharge from hospital was another strong risk factor and undoubtedly mirrors the influence of wound infection. A prolonged and difficult reconvalescence period was also related to joint sepsis as can be expected, because many patients with low-grade joint sepsis stated that they were suffering from pain immediately after the operation[20]. Such patients who are also at risk should have frequent check-ups at the outpatient department.

In conclusion, the identification of several risk factors for joint sepsis enables the orthopaedic surgeon to trace high risk patients. Patients with diabetes, a history of previous operations (especially fracture osteosynthesis), a breakdown of sterility and surgical reintervention and probably also reumatoid arthritis, are at risk for joint sepsis. There is some evidence that the application of gentamicin bone cement might reduce the incidence of joint sepsis[8] and it is therefore recommended in high risk patients. Patients with diabetes should be carefully prepared and monitored during the period of hospitalization.
If patients suffer from wound infection after the operation, they carry a very high risk of developing joint sepsis and should be given adequate antibiotic therapy. Antibiotic therapy should be guided by the results of wound cultures. Minor woundhealing problems do not form an indication for treatment. In the case of wound infection with a draining haematoma, surgical evacuation is indicated. Patients with an unhealed wound or a slow reconvalescence period should undergo frequent follow-up examinations after discharge from hospital.

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References

1. Andrews H J., Arden G.P., Hart G M , Owen J.W., Deep infection after total hip replacement. *J Bone and Joint Surg 63B. 53-57, 1981.*
2. Benson M.K.D., Hughes S.P.F., Infection following total hip replacement in a general hospital without special orthopaedic facilities. *Acta Orthop Scand. 46*: 968-978, 1975.
3. Donovan T.L., Gordon R.O., Nagel D.A., Urinary infections in total hip arthroplasty. Influences of prophylactic cephalosporins and catheterisation. J. *Bone and Joint Surg. 58A*: 1134-1137, 1976.

4. Fitzgerald R.H., Nolan D.R., Ilstrup D.M., van Scoy R.E., Washington II J.A., Coventry M.B., Deep wound sepsis following total hip arthroplasty. *J. Bone and Joint Surg. 59A*: 847-855, 1977.
5. Gristina A.G., Costerton J.W., Bacterial adherence and the glycocalyx and their role in musculoskeletal infection. *Orthop. Clin. of N. America 15*: 517-535, 1984.
6. Hill C., Mazas F., Flamant R., Evrard J., Prophylactic cefazolin versus placebo in total hip replacement. *Lancet 1*: 795-797, 1981.
7. Irvine R., Johnson B.L., Amstutz H.C., The relationship of genitourinary tract procedure and deep sepsis after total hip replacements. *Surg. Gyn. Obstet. 139*: 701-706, 1976.
8. Josefsson G., Lindberg L., Wiklander B, Systemic antibiotics versus gentamicin-containing bone cement in the prophylaxis of postoperative infection in total hip arthroplasty. *Clin. Orthop. 159*: 194-200, 1981.
9. Kamme C., Lindberg L., Aerobic and anaerobic bacteria in deep infection after total hip arthroplasty. Differential diagnosis between infectious and non-infectious loosening. *Clin. Orthop. 154*: 201-207, 1981.
10. Lidwell O.M., Clean air at operation and subsequent sepsis in the joint. *Clin. Orthop. 211*: 91-102, 1986.
11. Lidwell O.M., Lowbury E.J.L., Whyte W., Blowers R., Stanley S.J., Lowe D., Airborne contamination of wounds in joint replacement operations: the relation to sepsis rates. *J. Hosp. Inf. 4*: 111-132, 1983.
12. Lidwell O.M., Lowbury E.J.L., Whyte W., Blowers R., Stanley S.J., Lowe D., Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or total knee replacement: A randomized study. *Br. Med. J. 285*:10-14,1982.
13. Lidwell O.M., Lowbury E.J.L., Whyte W., Blowers R., Stanley S.J., Lowe D., Infection rates after operations for total hip or total knee-joint replacement: influence of ultraclean air, prophylactic antibiotics and other factors. *J. Hyg. Camb. 93*: 505-529, 1984.
14. Lynch M., Esser M.P., Shelley P., Wroblewski B.M., Deep infection in Charnley low-friction arthroplasty: comparison of plain and gentamicin-loaded cement. *J. Bone and Joint Surg. 69B*: 355-360, 1987.
15. McCue, The efficacy of double gloving as a barrier to microbial contamination during total joint arthroplasty. *Orthop.Trans.*: 371-372, 1980.
16. Nelson J.P., The operating room environment and its influence on deep wound infection. In *The hip: Proceedings of the 5th open scientific meeting of the hip society*, 129-146, 1977.
17. Nelson J.P., Glassburn A.R., Talbott R.D., McElhinney J.P., The effect of previous surgery, operating room environment, and preventive antibiotics on postoperative infection following total hip arthroplasty. *Clin. Orthop. 147*: 167-169, 1980.
18. Nelson C.L., The prevention of infection in total joint replacement surgery. *Rev. Inf. Dis.9*: 613-618, 1987.
19. Poss R., Thornhill T.S., Ewald F.C., Thomas W.H., Batte N.J., Sledge C.B., Factors influencing the incidence and outcome of infection following total joint arthroplasty. *Clin. Orthop. 182*: 117-126, 1984.
20. Rens van Th.J.G., Slooff T.J.J.H., The investigation of the painful total hip. In: *Complications of total hip replacement.* Ed.: Ling R.S.M. Churchill Livingstone 231-241, 1984.
21. Ryan G.B., Inflammation and localization of infection. *Surg. Clin. N. Am. 56*: 831-846, 1976.
22. Salvati E.A., Robinson R.P., Zeno S.M., Koslin B.L., Brause B.D., Wilson P.D., Infection rates after 3175 total hip and total knee replacements performed with and without a horizontal unidirectional filtered air-flow system. *J. Bone and Joint Surg. 64A*: 525-535, 1982.

23 Surin V V , Sundholm K , Backman L , Infection after total hip replacement *J Bone and Joint Surg 65B* 412-418, 1983
24 Trippel S B , Antibiotic-impregnated cement in total joint arthroplasty current concepts review *J Bone and Joint Surg 68A* 1297-1302, 1986
25 Wroblewski B M , Del Sel H J , Urethral instrumentation and deep sepsis in total hip replacement *Clin Orthop 146* 209-212, 1980
26 Wymenga A B , Van Horn J R , Theeuwes A , Muytjens H L , Slooff T J J H, Joint sepsis after infection prophylaxis with one or three doses of cefuroxime in 2651 hip replacements Submitted for publication

Chapter VI

Risk factors for joint sepsis in total knee replacement

A analysis of 362 operations

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Summary

Risk factors associated with joint sepsis were investigated in 345 patients who underwent 362 knee replacements in a prospective multicentre trial. The operations were performed at 22 hospitals with conventionally-ventilated operating theatres and all the patients recewed a short course of perioperatwe cefuroxime. After a mean of follow-up of 12 months, joint sepsis was diagnosed in 9 patients (2.5%).

The risk ratio (RR) for joint sepsis in patients with rheumatoid arthritis was 5.0 times higher and in patients who had undergone surgical reintervention 4.7 times higher than in patients without these conditions.

Patients with a woundinfection were 17.2 times more at risk for joint sepsis and patients who recewed antibiotics for woundproblems 20.8 times more. The risk was also higher in the presence of skin necrosis (RR=14.7) and wound dehiscence (RR=4.5), especially in combination with an additional woundhealing problem. Patients from whom a wound or blood culture was taken were 10.7 and 3.9 times more at risk, respectwely Patients who were discharged from hospital with an unhealed wound carried a high risk (RR=20.3) as well as patients with a painful and limited function at discharge (RR=7.0)

The application of gentamicin bone cement is recommended in high risk patients. It is also possible that this approach would be beneficial for all knee replacement patients, in view of the relative high joint sepsis rate, but further trials are needed to confirm this.

Early diagnosis and adequate antibiotic therapy is indicated in patients with high risk wound problems. Antibiotic treatment is not neccesary in the presence of a single minor woundproblem, drainage or hematoma. Significant skin defects should be closed by skingrafting or musculocutaneous flaps. Patients who are discharged from hospital with an unhealed wound or painful and limited knee function should undergo frequent follow-up examinations at the outpatients clinic.

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Introduction

Joint sepsis after total knee arthroplasty is still a major complication and it has devastating consequences[16]. It is the second most frequent reason for failure[14]. The operating theatre environment plays an important role in the incidence of joint sepsis. In conventionally-ventilated operating theatres, the incidence of joint sepsis is two to four times higher than in clean air. Moreover, 90-95% of all the cases of joint sepsis are initiated during the operation. It is possible to achieve a fourfold reduction by using perioperative antibiotics[15].
The individual patient characteristics also play an important role. The medical and orthopaedic diagnoses, previous operations, the type of prosthesis and the surgical techniques, all exert an influence on the risk of acquiring joint sepsis[5,17,18].
The purpose of this study was to investigate the risk factors which are associated with joint sepsis in 345 patients with 362 total knee replacements, all operated on in conventionally-ventilated operating theatres, with a short course of perioperative antibiotics.

Patients and methods

From July 1986 to July 1988, a prospective randomized controlled trial was performed at 22 hospitals with conventionally-ventilated operating theatres, in order to investigate the efficacy of one dose of cefuroxime (1500 mg i.v. at the induction of anaesthesia) in knee replacement. Patients receiving a three dose cefuroxime regimen (perioperative dose 1500 mg, subsequent doses of 750 mg i.v. after 8 and 16 hrs., respectively) served as a control. A relevant summary is given in this section, as details were reported elsewhere[23].
A total of 455 total knee replacements were eligible for entry into the trial, of which 58 were excluded. The most frequent reason for exclusion was the use of gentamicin-impregnated bone cement. This series therefore represents a rather homogeneous group of patients who underwent knee replacement procedures, as a number of high risk patients were excluded. Further exclusion criteria were the use of other antibiotics and former or current sepsis in the joint.
From the remaining 397 total knee hip replacements, 35 were withdrawn for the following reasons: the wrong type and/or dose of antibiotics had been administered, death (not sepsis-related) within 7 days of the operation or a second replacement, performed during the same period of hospitalization. This left 362 knee replacements (345 patients) for analysis.

In the analysis, the end point of participation in the follow-up was defined as reoperation or death, but a separate analysis was done on the reoperations (not for infection). The mean follow-up was 12 months and no patients were lost to follow-up.

In the one dose group (n=175), 3 patients suffered from joint sepsis (1.71%, 95% confidence limits 0.09-3.33) and in the three dose group 6 patients (3.20%, 95% confidence limits 0.63-5.77). The difference between the one dose group and the three dose group was -1.49% (95% confidence upper limit 1.78%). Definite conclusions about the equal efficacy of one dose of cefuroxime in knee replacement could therefore not be drawn, because the trial sample was too small.
The incidence in a simultaneous performed trial with 2651 hip replacements treated with the same prophylactic regimen was 0.64% [24].

Definitions

- Confirmed joint sepsis was defined as a positive culture at reoperation or a draining sinus.
- Strong evidence of joint sepsis was defined as four or more possible signs of sepsis (pain during weight-bearing and/or at rest, tenderness of the wound, fever, an abnormal X-ray with periostial reactions, progressive bone resorption, an increased ESR (20 mm above the preoperative value or > 35 mm), positive culture in the joint fluid aspiration, a positive arthrogram, a bone scan showing the typical signs of infection or an increased CRP.

- Wound infection in the postoperative period, was simply defined as erythema more than one centimetre from the incision.
- Minor postoperative woundhealing problems were defined as erythema of the wound less than one centimetre from the incision, pus suture, small wound dehiscence, necrosis of the wound edge and blisters.

- Distant infections were usually diagnosed on the basis of positive cultures. Urine cultures were considered positive if bacteriuria was present with more than 10^5 bacteria per ml. A few lung and skin infections were also diagnosed on a clinical basis.

Statistical analysis

Joint sepsis rates within subgroups were estimated as crude ratios. Univariate analysis of all the potential risk factors was performed with a chi-square test. From all the risk factors tested, only those with a p-value of $p <= 0.1$ were considered to be significant. These, and a few other interesting risk factors, are summarized in Tables Ia-d.
The number of times the risk for joint sepsis is increased can be expressed as the risk ratio (RR):

$$\text{RISK RATIO} = \frac{\%\,\text{JOINT SEPSIS WITH RISK FACTOR}}{\%\,\text{JOINT SEPSIS WITHOUT RISK FACTOR}}$$

As is it possible for risk factors to be related to each other, their importance can be overestimated in an univariate analysis. To overcome this problem, a multiple logistic regression analysis was used. This method identifies the risk factors whose influence is independent of any other simultaneously occurring risk factor(s) (Tables IIa-d). In this way, we identified separate risk factors which have an additive effect on the risk of joint sepsis, i.e. the more factors a patient has, the higher the risk of joint sepsis.
Four separate groups of risk factors were analysed: preoperative and perioperative risk factors (Ia), postoperative factors (Ib), culture results (Ic) and risk factors at discharge from hospital (Id). Within each section, a regression analysis was performed (Tables IIa-d).

Results

Joint sepsis

Joint sepsis was confirmed by a positive culture at reoperation or a draining sinus in 8 patients. Strong evidence was found in one. All these patients underwent reoperation for joint sepsis.

Preoperative and peroperative risk factors (Table Ia)

In the univariate analysis, the following preoperative factors were not found to be associated ($p > 0.1$) with joint sepsis: sex, age, the cefuroxime dose (one dose or three doses), the quetelet index (kg/m^2), physical condition, number of days in hospital before the operation, preoperative infections of the urinary tract, lung or skin, a urine sediment with more

than 5 leucocytes per field (400x) and the use of steroids.
Diabetes and previous surgery showed increased risk ratios but the differences did not reach significance ($p <= 0.1$). The orthopaedic diagnosis was clearly related to joint sepsis; patients with rheumatoid arthritis were much more at risk for joint sepsis than patients with arthrosis.

Analysis of the perioperative data showed that the use of (plain) bone cement, a breakdown of sterility, the degree of difficulty, the operation time, the amount of blood loss, the status of the surgeon (staff or resident) and the type of prosthesis (semi or non-constrained), were not related to joint sepsis.

The multiple logistic regression analysis of the most important preoperative and perioperative data identified rheumatoid arthritis as the only risk factor which acted independently. The risk was approximately five times increased (Table IIa).

Table Ia Univariate risk factor analysis: preoperative and peroperative data

Risk factor	n	Joint sepsis n (%)	risk ratio	p value #
diabetes	17	1 (5.88)	2.3	0.36
no diabetes	342	8 (2.32)	-	
rheumatoid arthritis	107	6 (5.94)	4.3	0.05
other	7	0 (0.00)	0.0	
arthrosis	248	3 (1.29)	-	
prosthesis	7	1 (14.29)	6.7	0.21
osteotomy	23	1 (4.17)	2.0	
other	49	1 (2.04)	1.0	
no previous operation	282	6 (2.13)	-	

(# = chi-square test, $p < = 0.1$ is significant)

Woundhealing and other postoperative factors (Table Ib)

The following factors were not found to be related to joint sepsis: the postoperative day of vacuum-drain removal, discharge from the vacuum-drain wound after removal of the drain and indwelling urinary catheters. Orthopaedic complications (n=9), such as nerve damage and fractures which were treated conservatively, did not relate to joint sepsis. Non-orthopaedic complications (n=11), the majority being cardiovascular, did not relate either. Five patients had non-orthopaedic operations (urinary and gastrointestinal tract), but none of them developed joint sepsis.

Patients with severe haematoma had an increased risk for joint sepsis. Minor woundhealing problems analysed as a group, were also related to joint sepsis. Further analysis of this group showed that particularly patients with skin necrosis at the wound edge and (to a lesser extend) wound dehiscence carried a high risk for joint sepsis. Only those patients with skin necrosis or wound dehiscence, who also had an additional wound problem, developed joint sepsis. Skin necrosis was not related to previous operations or rheumatoid arthritis. Single minor wound problems, such as erythema less than 1 cm from the incision, pus suture or blisters, did not relate to joint sepsis.
In the group of 12 patients with skin necrosis, 3 patients underwent additional attempts to close the skin defect, which succeeded in two and failed in one patient who developed joint sepsis.

Table Ib Univariate risk factor analysis: woundhealing and other postoperative factors

Risk factor		n	Joint sepsis n (%)	risk ratio	p value #
haematoma:	light	32	2 (3.13)	1.7	0.04
	moderate	49	1 (2.04)	1.1	
	severe	12	2 (14.29)	7.6	
	none	267	5 (1.87)	-	
minor woundhealing problems:					
absent:		294	5 (1.70)	-	0.05
present:		68	4 (5.88)	3.5	
	erythema < 1 cm	35	1 (2.86)	1.7	
	pus suture	2	- -	0	
	dehiscence	26	2 (7.69)	4.5	
	blisters	3	- -	0	
	skin necrosis	12	3 (25.00)	14.7	
wound drainage:					
absent:		294	5 (1.70)	-	0.05
present:		68	4 (5.88)	3.5	
	serous	51	3 (3.92)	2.3	
	blood	13	1 (7.69)	4.5	
	pus	4	1 (25.00)	14.7	
wound infection		13	3 (23.08)	13.4	0.00
no wound infection		349	6 (1.72)	-	
antibiotics (wound)		26	5 (19.23)	16.4	0.00
no antibiotics		336	4 (1.17)	-	

(# = chi-square test, p < = 0.1 is significant)

Patients with wound drainage were also more at risk. The presence of

serous drainage or blood, meant a moderate increase, but patients with pus had a very high risk.
Wound infection was a strong predictor of joint sepsis and often accompanied by other woundhealing problems. Patients who received antibiotics for woundhealing problems were even more at risk.

Multiple logistic regression analysis showed that an antibiotic administered for wound problems, was the strongest variable which acted independently (Table IIb1). When regression analysis was done without antibiotics, wound infection was identified as the strongest independent factor (Table IIb2). The other woundhealing problems such as haematoma and drainage exerted their influence largely in combination with prescription of antibiotics or wound infection.

Cultures of the wound and other sites (Table Ic)

Drain cultures did not relate to joint sepsis, whereas positive and (to a lesser extend) negative wound cultures did.
The most frequent site of distant infection was the urinary tract (18.2%) but there was no relation with joint sepsis. Patients with skin infections and patients from whom a blood culture was taken for high temperature or wound problems, were also at risk. Two patients with septicaemia (positive blood culture) did not develop joint sepsis.

Table Ic Univariate risk factor analysis wound and other cultures

Risk factor		n	Joint sepsis n (%)	risk ratio	p value #
wound culture.	negative	17	1 (5 88)	3 8	0 00
	positive	18	3 (16 67)	10 9	
	not done	327	5 (1 53)	-	
skin infection	present	6	1 (16 67)	7 4	0 02
	absent	356	8 (2 25)	-	
blood culture	negative	22	2 (9 52)	5 0	0 10
	positive	2	0 (0 00)	0.0	
	not done	338	7 (2 07)	-	

(# = chi-square test, p < = 0 1 is significant)

The multiple logistic regression analysis revealed that the wound culture and the blood culture both acted as independent risk factors (Table IIc). Validation showed that in the patients from whom a wound culture and/or a blood culture was taken (n=54), five (9.3%) suffered from joint

sepsis, whereas there were only four cases (1.3%) in the patients who did not undergo these tests.

Situation at discharge from hospital (Table Id)

An unhealed wound at discharge from hospital was a strong risk factor. An elevated temperature at discharge was less strongly related to joint sepsis. Patients with a painful knee and limited function at discharge carried an increased risk for joint sepsis. A prolonged and difficult reconvalescence period was also a meaningful predictive factor for joint sepsis.
The multiple logistic regression analysis revealed that an unhealed wound and, to a lesser extend, a painful knee with limited function, were risk factors which acted independently (Table IId). Validation of the data showed that in patients with these factors, five out of the 36 (10.2%) developed joint sepsis, versus only four out of the 326 (1.2%) without these factors.

Table Id Univariate risk factor analysis: situation at discharge

Risk factor		n	Joint sepsis n	(%)	risk ratio	p value #
wound not healed		13	4	(30.77)	21.5	0.00
healed		349	5	(1.43)	-	
temperature	elevated	13	1	(16.67)	7.4	0.02
	normal	356	8	(2.25)		
function limited,	pain	27	4	(14.81)	9.9	0.00
	pain-free	335	5	(1.49)	-	
reconvalescence	slow	42	4	(9.52)	6.1	0.00
	normal	320	5	(1.56)	-	

(# = chi-square test, $p <= 0.1$ is significant)

Mechanical reoperations

During the period of hospitalization and follow-up, 24 "mechanical" reoperations were performed for various reasons: 15 for patellofemoral problems (the majority being dislocations), two for fractures of the adjacent bone, one for prosthesis fracture, one for medial collateral ligament rupture, two arthrotomies for limited function, one haematoma evacuation, one revision for instability and one neurinoma excision.
Joint sepsis was diagnosed in nine of 338 patients (2.7%) without rein-

tervention versus three of 24 patients (12.5%, RR = 4.7) in this group after the second operation. In one of these patients, a tuberositas transfer for patellar dislocation was performed, after which a large haematoma with wound infection and subsequent joint sepsis developed. No perioperative antibiotics were given at reoperation. In the second patient, skin necrosis, wound infection and joint sepsis developed after two repair operations for traumatic patellar tendon rupture. In the third patient, adhesiolysis was performed for limited function five months after the index operation and subsequent wound and joint infection developed.

Table II Multivariate analysis of risk factors

	Beta	SE	risk ratio#
a Rheumatoid arthritis	1.6	0.7	5.0
b1 Antibiotics for wound	3.0	0.7	20.8
b2 Wound infection	2.8	0.8	17.2
c Wound culture done	2.4	0.8	10.7
Blood culture done	1.4	0.9	3.9
d Wound not healed	3.0	0.8	20.3
Pain + limited function	2.0	0.8	7.0

(a = preoperative/perioperative risk factor, b = postoperative wound problems, c = cultures, d = situation at hospital discharge, beta = regression coefficient, SE = standard error, # estimate of risk ratio = $e^{(beta)}$)

Discussion

In a prospective trial, 345 patients underwent 362 total knee replacements in conventionally-ventilated operating theatres, with a short course of systemic antibiotics. A number of risk factors were identified which acted independently in relation to joint sepsis, especially in the postoperative period.

Rheumatoid arthritis was an important risk factor for joint sepsis, which has also been found by other authors[5,6,8,15,16,18]. Diabetes and previous operations were not identified as being significant risk factors in this study contrary to others[5,8,14,18], but this may be due to the limited number that entered the study (Table Ia). Patients who underwent reoperation after the index arthroplasty ran approximately five times more risk, as 12.5% of these patients ended up with joint sepsis. In previously operated knees, low-grade sepsis must always be excluded, especially

with hardware in situ and multiple biopsies from interface tissue should be sent for culture as described by Kamme and Lindberg[11].
There is some evidence that gentamicin bone cement in combination with systemic antibiotics, reduces joint sepsis in hip replacement[10,16,21]. We therefore propose to use it in cemented knee replacement procedures in all risk patients with rheumatoid arthritis, diabetes and previous operations. But in view of the relative high incidence of joint sepsis in knee replacement as compared with hip replacement, even without risk factors, it might be beneficial for all cemented knee replacements. Further trials with gentamicin bone cement are needed to confirm this, in order to find methods of reducing joint sepsis when clean air operating theatre facilities are not available.

The 18% incidence of minor wound problems in our series was high but comparable with the rates mentioned in other reports (varying from 5% up to 25%)[7,9,12]. From the minor wound problems, only wound edge necrosis and wound dehiscence were clearly related to joint sepsis and only those patients who also suffered from other wound problems such as erythema or drainage developed joint sepsis. Secondary infection may have been initiated through these skin defects. Other papers[2,4,13] have reported 10-33% joint sepsis in patients with these wound problems. We could not confirm the relationship between necrosis and rheumatoid arthritis or previous surgery[1,6,19,20].
Insall[6] advised immobilizing the knee in the case of skin necrosis and awaiting spontaneous separation of the eschar, because early debridement might lead to the spread of infection to the deep fascial layers and the prosthesis. After that, skin grafting can be performed or, in the case of wound dehiscence, secondary closure can be performed. Vascularized musculocutaneous skin flaps should be used to salvage the joint if the necrosis is progressive[1,19,20].

Many authors have reported that delayed woundhealing is related to joint sepsis in knee replacement[2-4,8,12,17,18], but the relative importance of various woundhealing problems was not clear. In this study wound infection as well as skin necrosis or wound dehiscence in combination with other wound problems were found to be important postoperative riskfactors. Orthopaedic surgeons were correct in considering these latter patients without wound infection to be at risk for joint sepsis, because their prescription of antibiotics was more strongly related to joint sepsis than wound infection. Patients with single minor woundhealing problems, wound drainage or hematoma were not at risk for joint sepsis.

Early diagnosis and adequate antibiotic treatment is indicated in patients

with high risk wound problems in order to reduce the incidence of joint sepsis[15]. The antibiotic course should be guided by the results of wound cultures, because it is very likely that the pathogens cultured from the wound will also be present in the joint when reoperation is performed for joint sepsis[15]. There is no indication for antibiotic treatment in patients with a single minor wound problem, drainage or haematoma.
The increased risk for joint sepsis in patients who are discharged from hospital with an unhealed wound or with a painful knee with limited function, is also obvious and these patients should be followed-up by frequent outpatient visits.

In this study we were able to identify a number of important risk factors for joint sepsis in knee replacement. Patients with rheumatoid arthritis, a history of surgical reinterventions and probably also diabetes and previous surgery, carry a higher risk for joint sepsis. Additional gentamicin bone cement is recommended in (high) risk patients who undergo a cemented replacement and this may, in view of the relatively high rate of joint sepsis without risk factors, be beneficial for all patients.
Risk factors in the postoperative period were mostly related to woundhealing problems. Patients with wound infection and also patients who developed skin necrosis or wound dehiscence in combination with other woundhealing problems were very much at risk. Antibiotics should be prescribed for these patients and the course be guided by the wound culture results. There is no indication for antibiotic treatment in patients with a single minor woundhealing problem, wounddrainage or haematoma. Significant skin defects should be closed with skingrafting or musculocutaneous flaps.
Patients who are discharged from hospital with a painful and limited knee function or an unhealed wound should receive special adjunctive follow-up care.

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References

1 Bengtson S , Carlsson A , Relander M , Knutson K , Lidgren L., Treatment of the exposed knee prosthesis *Acta Ortop Scand 58* 662-665, 1987
2 Bengtson S , Knutson K , Lidgren L , Treatment of infected knee arthroplasty *Clin Orthop 245* 173-178, 1989
3 Bliss D G , McBride G G , Infected total knee arthroplasties *Clin Orthop 199* 207-214, 1985

4. Brodersen M.P., Fitzgerald R.H., Lowell F.A., Peterson F.A., Coventry M.B., Arthrodesis of the knee following failed total knee arthroplasty. *J. Bone and Joint Surg. 61A*: 181-185, 1979.
5. Grogan T.J., Dorey F., Rollins J., Amstutz H.C., Deep sepsis following total knee arthroplasty. *J. Bone and Joint Surg. 68A*: 226-234, 1986.
6. Insall J.N., Thompson F.M., Infections in total knee arthroplasty. In: *Infection in joint replacement surgery. Prevention and management.* Ed. N.S. Eftekhar, C.V. Mosby Co., St.Louis, 363-376, 1984.
7. Insall J., Norman Scott W., Ranawat C.J., The total condylar knee prosthesis. *J. Bone and Joint Surg. 61A*: 173-180, 1979.
8. Johnson D.P., Bannister G.C., The outcome of infected arthroplasty of the knee. *J. Bone and Joint Surg. 68B*: 289-291, 1986.
9. Jones E.C., Insall J.N., Inglis A.E., Ranawat C.J., Guepar knee arthroplasty and late complications. *Clin. Orthop. 140*: 145-152, 1979.
10. Josefsson G., Lindberg L., Wiklander B., Systemic antibiotics versus gentamicin-containing bone cement in the prophylaxis of postoperative infection in total hip arthroplasty. *Clin. Orthop. 159*: 194-200, 1981.
11. Kamme C., Lindberg L., Aerobic and anaerobic bacteria in deep infection after total hip arthroplasty. Differential diagnosis between infectious and non-infectious loosening. *Clin. Orthop. 154*: 201-207, 1981.
12. Kaufer H., Matthews L.S., Spherocentric arthroplasty of the knee. *J. Bone and Joint Surg. 63A*: 545-559, 1981.
13. Knutson K., Hovelius L., Lindstrand A., Lidgren L., Arthrodesis after failed knee arthroplasty. *Clin. Orthop. 191*: 202-211, 1984.
14. Knutson K., Lindstrand A., Lidgren L., Survival of knee arthroplasties. A nation-wide multicenter investigation of 8000 cases. *J. Bone and Joint Surg. 68B*: 795-803, 1986.
15. Lidwell O.M., Lowbury E.J.L., Whyte W., Blowers R., Stanley S.J., Lowe D., Infection rates after operations for total hip or total knee-joint replacement: influence of ultraclean air, prophylactic antibiotics and other factors. *J. Hyg. Camb. 93*: 505-529, 1984.
16. Lynch M., Esser M P., Shelley P., Wroblewski B.M., Deep infection in Charnley low-friction arthroplasty: comparison of plain and gentamicin-loaded cement. *J. Bone and Joint Surg. 69B*: 355-360, 1987.
17. Petty W., Bryan R.S., Coventry M.B., Peterson L.F.A., Infection after total knee arthroplasty. *Orthop.Clin. N. Am. 6(4)*: 1005-1014, 1975.
18. Rand J.A., Fitzgerald R.H., Diagnosis and management of the infected total knee arthroplasty. *Orthop. Clin N. Am. 20 (2)*: 201-210, 1989.
19. Saliban A.H., Anzel S.H., Salvage of an infected total knee prosthesis with medial and lateral gastrocnemius muscle flaps. *J. Bone and Joint Surg. 65A*: 681-684, 1983.
20. Sanders R., O'Neil T., The gastrocnemius myocutaneous flap used as a cover for the exposed knee prosthesis. *J. Bone and Joint Surg. 63B*: 383-386, 1981.
21. Trippel S.B., Antibiotic-impregnated cement in total joint arthroplasty: current concepts review. *J. Bone and Joint Surg. 68A*: 1297-1302, 1986.
22. Walker R.H., Schurman D.J., Management of infected total knee arthroplasties. *Clin. Orthop. 186*: 81-89, 1984.
23. Wymenga A.B., Van Horn J.R., Theeuwes A., Muytjens H., Slooff T.J.J.H., Joint sepsis after infection prophylaxis with one or three doses of cefuroxime in 362 knee replacements. Submitted for publication.
23. Wymenga A.B., Van Horn J.R., Theeuwes A., Muytjens H., Slooff T.J.J.H., Joint sepsis after infection prophylaxis with one or three doses of cefuroxime in 2651 hip replacements. Submitted for publication.

Chapter VII

The relation between wound, urine cultures and joint sepsis after hip and knee replacement

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Summary

The relation between wound and urine cultures was analysed in 2651 hip replacements (2547 patients) and 362 knee replacements (345 patients), operated on in conventionally-ventilated operating theatres, with perioperative infection prophylaxis of one dose or three doses of cefuroxime.

In 26 patients with joint sepsis (17 hip replacements and 9 knee replacements) S. aureus (42%), S. epidermidis (12%), gram-negative bacteria (24%) and anaerobic bacteria (4%) were identified as the causative agents. The bacterial spectrum was covered sufficiently by cefuroxime.

Joint sepsis was preceded by wound infection in 12 out of the 26 patients with this complication. When, in hip replacement, S. aureus, Gram-negative and other organisms were cultured from the postoperative wound, the risk for joint sepsis was increased 24, 17 and 10 times, respectively. S. epidermidis was not related to joint sepsis. In knee replacement there was no relation with S.aureus and S.epidermidis but the risk was 17 times increased with gram-negative organisms and 15 times increased with other organisms in the wound culture.

Perioperative joint cultures were positive in 4.2% but were not related to joint sepsis. Drain cultures were positive in 15% and related to joint sepsis, but the wound culture was considered to be far more reliable. Routine perioperative and drain cultures are therefore not indicated in primary joint replacement.

Postoperative urinary tract infections occurred in 15% of the patients. There was an increased risk for joint sepsis in hip replacement, but this could not be explained by early postoperative haematogenous bacterial seeding. Urinary tract infections were strongly related to the use of indwelling catheters and the incidence increased with time. Removal before the third day is recommended, because five patients in this study developed septicaemia with a catheter which had been in situ for more than 72 hours.

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Introduction

Systemic perioperative antibiotics are a very effective means of reducing the incidence of joint sepsis in conventionally-ventilated operating theatres, by a factor of 4 to 6 times[1,2,3]. No differences were found between 14 days and 1 day of antibiotic prophylaxis and 5 days and 1 day[4,5].
In a recent multicentre trial, the efficacy of one dose of perioperative cefuroxime in hip and knee replacement was compared to a three dose regimen[6,7]. The purpose of this study was to analyse the relation between wound and urine cultures and later joint sepsis in the patient population of this trial.

Patients and methods

From July 1986 to July 1988, a prospective randomized controlled trial was performed at 27 hospitals with conventionally-ventilated operating theatres, in order to evaluate the efficacy of a single perioperative dose of cefuroxime (1500 mg i.v. at the induction of anaesthesia) in hip and knee replacement. A three dose cefuroxime regimen, comprising an additional 750 mg i.v. after 8 and 16 hours, respectively, served as a control.
As a detailed report has been published elsewhere[6,7], only a relevant summary is presented in this section. A total of 3074 hip replacements and 455 knee replacements entered the trial, of which 278 hips and 58 knees were excluded. The most frequent reason for exclusion was the use of gentamicin-impregnated bone cement. From the remaining 2796 hip and 397 knee replacements, 145 and 35 were withdrawn, respectively. The main reasons were the administration of the wrong type and/or dose of antibiotics, death within 7 days of the operation or a second operation within the same period of hospitalization. This left 2651 hip replacements (2547 patients) and 362 knee replacements (345 patients) for analysis. This series represents a rather homogeneous group of patients who underwent replacement surgery, as a number of high risk patients were excluded.
The follow-up ended with joint sepsis, reoperation or death. The mean follow-up was 13 months for the hip group and 12 months for the knee group.

Definitions

- Joint sepsis was defined as a positive culture at reoperation or a draining sinus.

- Strong evidence of joint sepsis was defined as four or more possible signs of sepsis at follow-up (pain on weight-bearing and/or at rest, tenderness of the wound, fever, an X-ray with periostial reactions or progressive bone resorption, an increased ESR (20 mm above the preoperative value or > 35 mm), positive joint aspiration, a positive arthrogram, a bone scan indicating infection or an increased CRP).

- Wound infection in the postoperative period was defined as erythema of more than one centimetre measured from the incision.
- Minor woundhealing problems were defined as erythema of less than 1 cm measured from the incision, pus suture, small wound dehiscence, necrosis of the wound edge and blisters.
- Distant infections were diagnosed on the basis of positive cultures. A urinary tract infection was defined as bacteriuria of more than 105 bacteria/ml. Blood cultures of *Staphylococcus epidermidis* were only considered to be positive when cultured at least twice. A few skin, pulmonary and other infections were also diagnosed on a clinical basis.

Results

The most important results of the trial are summarized in Table I.

Table I Wound infection, wound cultures and distant infections in the one dose and three dose group (hip and knee replacements)

	HIP REPLACEMENT			KNEE REPLACEMENT		
	1 dose n=1324	3 doses n=1327	total (%) n=2651	1 dose n=175	3 doses n=187	total (%) n=362
haematoma (l/m/s)#	127/99/28	145/82/44	525 (20.0)##	19/23/5	13/26/9	97 (26.8)
minor wound probl.	169	166	335 (12.6)	33	35	68 (18.8)
wound drainage	166	178	344 (13.0)	30	38	68 (18.8)
wound infection	25	31	56 (2.1)	4	9	13 (3.6)
joint sepsis	11	6	17 (0.64)	3	6	9 (2.5)
positive wound cult.	43	48	91 (3.4)	10	8	18 (5.0)
positive drain cult.	65	57	122 (4.6)	12	6	18 (5.0)
urinary tract inf.	201	194	395 (14.9)	32	34	66 (18.2)
skin inf.	31	26	57 (2.2)	2	4	6 (1.7)
pulmonary inf.	18	20	38 (1.4)	3	5	8 (2.2)

(# = light/moderate/severe, ## = $0.05 < p < 0.10$, no other significant differences)

There were no significant differences between the one dose groups and the three dose groups with respect to woundhealing problems and wound infections. The number of positive wound cultures and drains

did not differ significantly. The incidence of remote infections was not influenced by one dose or three doses.

Joint sepsis and wound infections

Joint sepsis was diagnosed in twenty-six patients, 17 (0.64%) in the hip and 9 (2.45%) in the knee group. Cultures of the joint at reoperation for joint sepsis were taken in 22 patients and in one patient joint fluid from an aspiration was cultured *Staphylococcus aureus*. Most causative microorganisms were gram-positive microorganisms. *S. aureus* was isolated in 42%, *S. epidermidis* in 12%, gram-negative species in 24% and anaerobe species in 4% (Table V).
Early postoperative wound infection preceded joint sepsis in 12 out of the 26 patients with this complication, minor woundhealing problems preceded joint sepsis in six and light haematoma in two patients. In six patients, postoperative woundhealing was uneventful (Table II).

Table II Preceding postoperative woundhealing problems in joint sepsis

Woundhealing problem	HIP (n=17)	KNEE (n=9)
wound infection	9 (4)#	3 (1)#
minor woundhealing problems	3 (2)#	3 (2)#
slight haematoma	1	1
uneventful woundhealing	4	2

(# = number of patients who also had haematoma)

The incidence of joint sepsis after a positive wound culture was greatly increased and was found to be related to the species of microorganism isolated from the postoperative wound (Table III). The risk of joint sepsis in hip replacement after the isolation of *S. aureus*, gram-negative and other species was increased 24, 17 and 10 times when compared to patients without wound cultures, respectively. This relationship was not found with *S. epidermidis*.
The risk of sepsis in knee replacement was not increased after the isolation of *S. aureus* and *S. epidermidis*, but the risk was 17 times increased with gram-negative species and 15 times with other species.
The same bacterial species were isolated at reoperation from four out of the six postoperative wound cultures of patients who later developed joint sepsis of the hip and in one out of the three knee patients.

Table III Risk of joint sepsis after isolation of S aureus and other microorganisms from the postoperative wound, calculated per isolate

	HIP REPLACEMENT cultures	joint sepsis		KNEE REPLACEMENT cultures	joint sepsis	
	n	n	(%)	n	n	(%)
POSITIVE CULTURE	92	6	(6 5)	18	3	(16 6)
S aureus	38	4	(10 5)	4	0	(0 0)
S epidermidis	35	0	(0 0)	7	0	(0 0)
Gram-negative	27	2	(7 4)#	4	1	(25 0)$
other	44	2	(4 6)##	9	2	(22 0)$$
NEGATIVE CULTURE	67	0	(0 0)	17	1	(5 9)
NO CULTURE	2492	11	(0 4)	327	5	(1 5)

(# = E coli and Proteus, Pseudomonas sp and Proteus, ## = group D streptococcus and S viridans, $ = Enterobacter, $$ = Peptococcus, Bacillus sp and Corynebacterium sp)

At follow-up, the majority of patients with joint sepsis presented with a draining wound or a sinus; only four had a normal wound. Most patients were diagnosed within three months of hospital admission (Table IV).

Table IV Presentation at follow-up and time of diagnosis

Presentation at follow-up	hip n=17	knee n=9	Time definite diagnosis	hip n=17	knee n=9
sinus	9	4	1 month	9	3
draining wound	3	2	3 months	-	3
erythema/tenderness	1	3	4 months	1	1
normal wound	4	-	5 months	2	1
			10 months	-	1
			14 months	2	-
			18 months	1	-
			24 months	1	-

Perioperative cultures

The microorganisms grown in perioperative joint cultures are presented in Table V. Only 26 out of the 622 cultures (4.2%) were positive. None of the patients with positive perioperative cultures developed joint sepsis. The majority of the bacterial species belonged to the skin flora.

Table V Microorganisms grown in perioperative cultures from postoperative wound, drain, urine and joint sepsis

	peri-operative	wound	drain	urine	joint sepsis
SKIN ORGANISMS:					
S. aureus	2	42	12	6	11
S. epidermidis	17	42	96	17	3
Corynebacterium spp.	1	12	2	4	-
S. viridans	1	3	5	4	-
Bacillus spp.	-	2	4	-	-
Peptococcus spp.	-	1	-	-	1
P. acnes	1	1	-	-	-
Haemolytic streptococci	-	1	-	-	-
Group B streptococci	-	1	-	4	-
Branhamella cattharalis	-	1	-	-	-
Moraxella	-	1	-	-	-
Fungus	2	-	-	-	-
INTESTINAL AND OTHER ORGANISMS:					
Group D streptococci	-	23	16	102	-
E. coli	-	4	-	285	2
Proteus spp.	1	8	3	53	1
Klebsiella spp.	-	1	-	30	-
Pseudomonas spp.	1	6	3	24	-
Enterobacter spp.	-	5	2	12	3
Citrobacter spp.	-	1	-	3	-
Gram-negative rods	-	2	2	5	-
Bacteroides spp.	-	1	-	-	-
Acinetobacter spp.	-	4	4	2	-
Mixed infections#	-	4	1	17	-
no full data available	-	-	-	18	-
positive cultures:	26	109	140	455	20
number of cultures	622	194	939	766	23

(# = more than 3 species)

Vacuum-drain cultures

At a number of hospitals, drain cultures were performed routinely and 15.3% of 806 cultures were positive in hip replacement. In knee replacement, 18 out of 133 (13.5%) were positive. The majority of the cultured microorganisms belonged to the flora of the skin. There was a significant relationship between positive drain cultures and joint sepsis in hip replacement but not in knee replacement (Table VIa). In three cases in the hip replacement group, the same species were recovered from the postoperative drain culture and in later joint sepsis at reoperation (Table VIb).

The incidence of positive cultures was higher when the drains remained in situ for several days. There were 14.7% (132/909) positive cultures from drains removed in the first three days, versus 31.0% (9/29) from drains removed after the third day (x^2-test: p=0.03).

Table VI Vacuum-drain cultures

Table VIa Relationship between drain cultures and later joint sepsis

	HIP REPLACEMENT			KNEE REPLACEMENT		
	cultures	joint sepsis		cultures	joint sepsis	
	n	n	(%)	n	n	(%)
positive	122	5	(4.10) *	18	0	(0 00)
negative	684	3	(0 44)	115	4	(3.48)
not done	1845	9	(0.49)	228	5	(2.18)

(* x^2-test = 0.00)

Table VIb Isolates from drain cultures and later joint sepsis (hip replacement)

VACUUM-DRAIN CULTURE	JOINT SEPSIS
Pseudomonas + Proteus	Proteus
S. aureus + Streptococ D	S aureus
Enterobacter	Enterobacter
Gram neg rods	S. aureus
S epidermidis	Enterobacter
negative	S. epidermidis
negative (2x)	negative (2x)

Urinary tract infections

The incidence of postoperative urinary tract infections did not differ in the one dose groups and the three dose groups and was fairly similar in both hip and knee replacements (15% and 18%, respectively; Table I). The microorganisms are shown in Table V. The relationship between the presence and duration of urinary catheters and urinary tract infection (UTI) was significant, the incidence rose to 48% after more than three days (Table VII). The incidence of postoperative UTI was more than double in female patients (17%) when compared to males (7%).

Table VII Relationship between urinary catheters and postoperative urinary tract infection (replacements)

	no UTI	UTI	(%)	TOTAL
no catheter	1367	81	(5.6)	1448
< 24 hrs	430	80	(15.7)	510
24-48 hrs	394	73	(15.6)	467
48-72 hrs	156	30	(16.1)	186
> 72 hrs	211	191	(47.6)	402
total	2558	455	(15.1)	3014

(x^2-test: $p < 0.001$)

Hip replacement patients with postoperative UTI were significantly more at risk for joint sepsis[6,33]. From the 395 hip replacements with a positive urine culture, nine (2.28%) developed joint sepsis, versus eight out of the 2256 replacements without a positive culture (0.36%).
Microorganisms cultured from the urine did not match those cultured from the infected joint, except in one patient. From this patient, we isolated *E. coli* in the urine postoperatively and later in the joint, but documented haematogenous seeding of *E. coli* from the urinary tract occurred five months after the operation and not in the early postoperative period. The relationship in hip replacement, between positive urine cultures in the postoperative period and later joint sepsis, is therefore not a causal one.
Enterobacter was cultured from a draining wound of a patient who underwent knee replacement. The wound did not heal and at reoperation *Enterobacter* and *E. coli* were isolated. *E. coli* may have invaded the wound secondarily after a urinary tract infection with this microorganism.

Septicaemia

In 11 patients (0.4%) blood cultures were positive during the period of hospitalization. Only one patient with postoperative *S. aureus* septicaemia from an unidentified origin later developed joint sepsis. The urinary tract was the origin of septicaemia in five patients, all of whom had an indwelling urinary catheter for longer than 72 hours. In the remaining cases, septicaemia originated from infected packed cells, pneumonia, an infected cardiac catheter tip, sacral decubitus and the biliary tract.

Discussion

We were unable to establish that a single dose of cefuroxime was as equally effective as a three dose regimen, because the incidence of joint sepsis was low and possible range of incidences was too wide. A longer follow-up, with more diagnoses of joint sepsis is needed to draw definite conclusions. The results have been discussed elsewhere[6,7]. The prophylaxis regimen did not significantly influence the incidence of woundhealing problems, wound infection and distant infections during the period of hospitalization.

Joint sepsis and wound infection

The identified causative agents in joint sepsis, *S. aureus, S. epidermidis, E. coli, Proteus mirabilis, Peptococcus and Enterobacter*, were usually sensitive to cefuroxime. The sensitivity of *Enterobacter* strains has been known to vary, but those isolated from three patients with joint sepsis were susceptible to cefuroxime. The bacterial spectrum was therefore considered to be sufficient.
The incidence of Gram-positive, Gram-negative and anaerobe microorganisms isolated from patients with joint sepsis was well within the range of other studies[8-12], although we isolated relatively few *S. epidermidis* and anaerobes. This may be due the follow-up period of one year, because joint sepsis with these organisms often runs a subclinical course[13,14].

From the postoperative wound we often cultured skin flora. The isolation of *S. epidermidis* in wound cultures was not related to joint sepsis. However, the isolation of *S. aureus*, Gram-negative and other bacteria considerably increased the risk of joint sepsis in hip replacement and gram-negative and other bacteria in knee replacement.
The number of isolates with *S. aureus* and group D *streptococci* was relatively high. The latter organism might be enhanced by cefuroxime because it is resistant to the drug, but short antibiotic prophylaxis is unlikely to exert much influence on microbial wound flora, especially as a significant percentage of postoperative (superficial) wound infection is later acquired on the hospital ward[15].

In 77% of the patients, joint sepsis was preceded by wound infection or other wound problems. In a large multicentre study, Lidwell et al. found woundhealing problems in 40% of the patients with joint sepsis[15]. As patients with wound infection are very much at risk for later joint sepsis[15,33,34] and the organisms found in postoperative wound infection and later joint sepsis are often similar, they should receive bactericidal

antibiotic treatment which is guided by the wound cultures.

Operative cultures

The percentage of positive perioperative joint cultures is known to depend on the culture technique, the level of air contamination[16], the use of antibiotics[17], previous surgery[18] and the time of sampling during the operation. In primary joint replacement, there is an inconsistent relationship between positive cultures and joint sepsis[1,18,19-22]. We did not find a relationship with joint sepsis and we agree with Rand[22] that cultures performed in primary replacement are of limited value.
In revision surgery, the risk of joint sepsis is increased after positive perioperative cultures[18 22 24]. However, one culture does not provide conclusive evidence, because false positive results frequently occur. It is only possible to differentiate between sepsis and loosening by taking five or more periprosthetic tissue biopsies for culturing (each taken with a different pair of sterile forceps). Growth in one or two samples is a strong indication of contamination, whereas growth in all five biopsies is a strong indication of joint sepsis. Systemic perioperative antibiotics should not be administered until all the biopsies have been taken[10,25].

Drain cultures

The incidence of positive vacuum-drain cultures in this series was about 15% for hip and knee replacements. Other authors have reported percentages from 5.8% to 9.2%[21 26 27] and most of the microorganisms belonged to the skin flora group. Our results confirmed that there were more positive cultures if the drains were left in situ longer[21 26].
In a few patients, similar pathogens were cultured from the drains and the joint in the case of sepsis. In many others, skin flora was cultured because it is difficult to keep the drain tip sterile during removal from the drain wound.
When a surgeon requires information on the microbiology of the surgical wound, the wound culture is a far more reliable indicator of the risk for joint sepsis. Routine drain cultures can therefore be abandoned.

Urinary tract infection

We found a 15 to 18% postoperative incidence of urinary tract infection. This is well within the range of those reported by other authors, who found a rate of 4 to 26% in joint replacement[1,20,21,27]. Lower incidences have been found in series in which the antibiotic prophylaxis was prolonged over several days[1,28]. With our short prophylaxis, we did not

find an increased incidence of *Pseudomonas* and *Enterobacter* as other authors did[28] after the prolonged use of cefalosporin.
We could confirm that most urinary tract infections are catheter- related and that the incidence increases with time[28 29]. Catheter removal before the third day is advised, as five patients developed septicaemia from the urinary tract after the catheter had been left in situ for longer than 72 hours.
Haematogenous seeding in the early postoperative period did not occur, although several other authors have reported this complication[28 30 32]. The relationship between postoperative urinary tract infection and joint sepsis in this series [33] was therefore not a causal one. In one patient who underwent knee replacement and developed an infected draining wound, secondary contamination may have originated from the urinary tract.

In 26 patients with joint sepsis, *S. aureus* (42%), *S. epidermidis* (12%), gram-negative bacteria (24%) and anaerobic bacteria (4%) were identified as causative agents. Cefuroxime provided adequate coverage of this bacterial spectrum.
Wound infection preceded later joint sepsis in 12 out of the 26 patients with this complication. If *S. aureus*, gram-negative and other organisms were cultured from the postoperative wound, the risk for joint sepsis increased 23, 17 and 10 times, respectively. *S. epidermidis* was not related to joint sepsis. In knee replacement the risk was 17 times increased after isolation of gram-negative organisms and 15 times after other speciae and there was no relation with *S. aureus* and *S. epidermidis*.
Perioperative cultures were positive in 4.2% but were not related to joint sepsis. Positive drain cultures did relate, but the wound culture was considered to be far more reliable. Routine perioperative and vacuum-drain cultures do not provide any useful additional information.
Postoperative urinary tract infections occurred in 15% of the patients. There was an increased risk for joint sepsis, but this could not be explained by early postoperative haematogenous bacterial seeding. The urinary tract infections were strongly related to the use of indwelling catheters. Removal of the catheter before the third day is recommended, as five of the patients in this study developed septicaemia after the catheter had been in situ for more than 72 hours.

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References

1 Hill C , Mazas F , Flamant R , Evrard J , Prophylactic cefazolin versus placebo in total hip replacement *Lancet I* 795-797, 1981

2 Ericsson C , Lidgren L , Cloxacillin in the prophylaxis of postoperative infections of the hip *J Bone and Joint Surg 55A* 808-813, 1973

3 Lidwell O M , Lowbury E J L , Whyte W , Blowers R , Stanley S J , Lowe D , Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement A randomized study *Br Med J 285* 10-14, 1982

4 Pollard P , Hughes S P F , Scott J E , Evans M J , Benson M K D , Antibiotics prophylaxis in total hip replacement *Br Med J 1* 708-709,1979

5 Heydemann J S , Nelson C L , Short-term preventive antibiotics *Clin Orthop 205* 184-187, 1986

6 Wymenga A B , Van Horn J R , Theeuwes A , Muytjens H L , Slooff T J J H , Joint sepsis after infection prophylaxis with one or three doses of cefuroxime in 2651 hip replacements A randomized controlled multicentre study Submitted for publication

7 Wymenga A B , Van Horn J R , Theeuwes A , Muytjens H L , Slooff T J J H , Joint sepsis after infection prophylaxis with one or three doses of cefuroxime in 362 knee replacements A randomized controlled multicentre study Submitted for publication

8 Carlsson A S, Josefsson G , Lindberg L , Revisions with gentamicin-impregnated cement for deep infections in total hip arthroplasties *J Bone and Joint Surg 60A* 1059-1064, 1978

9 Whyte W , Hodgson R , Tinkler J , Graham J , The isolation of bacteria of low pathogenicity from faulty orthopaedic implants *J Hosp Inf* 2 219-230, 1981

10 Lidwell O M , Lowbury E J L , Whyte W , Blowers R , Stanley S J , Lowe D , Bacteria isolated from deep joint sepsis after operation for total hip or knee replacement and the sources of the infections with staphyloccus aureus *J Hosp Inf 4* 19-29, 1983

11 Inman R D , Gallegos K V , Brause B D , Redecha P B , Christian C L , Clinical and microbial features of prosthetic joint infection *Am J Med 77* 47-53,1984

12 Buchholz H W , Elson R A A , Wegelbrech E , Lodenkamper H , Rottger J , Siegel J , Management of deep infection of total hip replacement *J Bone and Joint Surg 63B* 342-353, 1981

13 Blomgren G , Hematogenous infection of total joint replacement *Acta Orthop Scand (Suppl 187) 52* 7-63, 1981

14 Sanderson P J , The choice between prophylactic agents for orthopaedic surgery *J Hosp Inf 11 (suppl C)* 57-67, 1988

15 Lidwell O M , Lowbury E J L , Whyte W , Blowers R , Stanley S J , Lowe D , Infection and sepsis after operations for total hip or knee joint replacement Influence of ultraclean air, prophylactic antibiotics and other factors *J Hyg Cambr 93* 504-529, 1984

16 Nelson J P , Operating room environment clean rooms and personnel-isolator systems In *Infection in joint replacement surgery Prevention and management* Ed N S Eftekhar, C V Mosby, 166-178, 1984

17 Lidwell O M , Lowbury E J L , Whyte W , Blowers R , Stanley S J , Lowe D , Airborne contamination of wounds in joint replacement operations the relationship to sepsis rates *J Hosp Inf 4* 111-131, 1983

18 Tietjen R , Sunchfield F E , Michelsen C B , The significance of intracapsular cultures in total hip operations *Surg Gyn Obst 144* 699-702, 1977

19 Fitzgerald R H , Nolan D R , Ilstrup D M , Van Scoy R E , Washington II J A.,

Coventry M.B., Deep wound sepsis following total hip arthroplasty. *J. Bone and Joint Surg. 59A*: 847-855, 1977.
20. Surin V.V., Sundholm K., Backman L., Infection after total hip replacement with special reference to a discharge from the wound. *J. Bone and Joint Surg. 65B*: 412-418, 1983.
21. Mulier J.C., Cheng N., van Tournhout B., Vandepitte J., Debryune H., Effect of combined use of a clean air system and one day prophylactic administration of cefamandole in total hip replacement. *Arch. Orthop. Traum. Surg. 98*: 29-33, 1981.
22. Rand J.A., Fitzgerald Rr.H., Diagnosis and management of the infected total knee arthroplasty. *Orthop. Clin. NAm. 20(2)*: 201-210, 1989.
23. Dupont J.A., Significance of operative cultures in total hip arthroplasty. *Clin. Orthop.211*: 122-127,1986.
24. Ritter M.A., Stringer E.A., Intraoperative wound cultures: Their value and long-term effect on the patient. *Clin. Orthop. 155*: 180-185, 1981.
25. Kamme C.K., Lindberg L., Aerobic and anaerobic bacteria in deep infections after total hip arthroplasty. *Clin. Orthop. 154*: 201-207, 1981.
26. Willet K.M., Simmons C.D., Bentley G., The effect of suction drains after total hip replacement. *J. Bone and Joint Surg. 70B*: 607-610, 1988.
27. Evrard J., Doyon F., Acar J.F., Salord J.C., Mazas F., Flamant R., Two-day cefamandole versus five-day cephazolin in 965 total hip replacements. *Int. Orthop. 12*: 69-73, 1988.
28. Donovan T L., Gordon R.O., Nagel D.A., Urinary tract infections in total hip arthroplasty. *J. Bone and Joint Surg. 58A*: 1134-1137, 1976.
29. Stamm W.E., Nosocomial urinary tract infections. In: *Hospital infections*, Eds. Benett J.V and Brachman P.S., Little, Brown and Co., Boston/Toronto, 375-384, 1986.
30. Wroblewski B.M., Del Sel H.J., Urethral instrumentation and deep sepsis in total hip replacement. *Clin. Orthop 146*: 208-212, 1980.
31. Benson M.K.D., Hughes S P.F., Infection following total hip arthroplasty in a general hospital without special orthopaedic facilities. *Acta Orthop. Scand. 46*: 968-978, 1975.
32. Irvine R., Johnson B.L., Amstutz H.C., The relationship of genitourinary tract procedures and deep sepsis after total hip replacement. *Surg. Gyn. Obstet. 139*: 701-706, 1974.
33. Wymenga A.B., Van Horn J.R., Theeuwes A., Muytjens H.L., Slooff T.J.J.H., Risk factors for joint sepsis in hip replacement. Submitted for publication
34. Wymenga A.B., Van Horn J R., Theeuwes A., Muytjens H.L., Slooff T.J.J.H., Risk factors for joint sepsis in knee replacement. Submitted for publication.

Chapter VIII

The use of additional antibiotics after a single dose or three doses of perioperative cefuroxime prophylaxis in hip and knee replacement

A report on 2651 hip and 362 knee replacements

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Summary

We analysed the amount of additional antibiotics prescribed after hip and knee replacement surgery during which perioperative infection prophylaxis had been administered either as one dose or three doses of cefuroxime. The Defined Daily Dose (DDD) methodology for measuring drug use was employed. A total of 2651 hip and 362 knee replacements were performed: 1502 patients received a single perioperative dose of cefuroxime and 1511 received three perioperative doses of cefuroxime.
No relevant differences were observed between the groups who received a single dose and the groups who received three perioperative doses of cefuroxime with respect to the total amount, the type, the indication and duration of additional antibiotic therapy
Additional antibiotics were used in 21% of the patients after hip replacement and in 31% after knee replacement. An amount of 11.4 DDD per 100 bed days was administered in hip replacement and 15.7 DDD per 100 bed days in knee replacement. For wound problems, 3.8 and 6.9 DDD per 100 bed days were given in the hip and knee replacement groups, respectively. For distant infection, such as in the urinary tract, 6 5 DDD per 100 bed days were administered in both the hip and the knee group. The duration of antibiotic therapy varied only in relation to the indication The antibiotics most frequently prescribed were penicillin (43-50%), sulfonamides (18%), cephalosporins (10-16%) and nitrofurantoin (8-13%); drug use was found to be related to the type of infection.

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Introduction

During the past decades, various trials have demonstrated that a short perioperative course of antibiotics for the prevention of infection is effective in several surgical procedures and even a single dose has been advocated in selected cases[1,2]. In joint replacement surgery, no difference was found between 14, 7 and 1 day[3,4] and 5 and 2 days of prophylaxis[5]. Recently, a prospective randomized controlled trial was performed in order to compare the efficacy of a single perioperative dose of cefuroxime in hip and knee joint replacement surgery, to a three dose regimen which also served as a control[6,7].
The purpose of this study was to uncover details concerning the total amount, type, indication and duration of additional antimicrobial treatment used after a single dose or three doses of perioperative cefuroxime prophylaxis in hip and knee replacement surgery.

Patients and methods

From July 1986 to July 1988, a prospective randomized controlled trial was performed at 27 Dutch hospitals with conventionally-ventilated operating theatres. In the single dose group and the three dose group, 1500 mg of cefuroxime were administered intravenously at the induction of anaesthesia. In the three dose group, the patients also received 750 mg of cefuroxime i.v. after 8 and 16 hours, respectively.
Patients who underwent total hip replacement, hemiarthroplasty of the hip or total knee replacement, were eligible for participation in the study. The most important exclusion criteria were the use of antibiotics less than 48 hours before the operation, the administration of other perioperative antibiotics than cefuroxime, former or current infections in the joint and the use of gentamicin-impregnated bone cement; the latter was often used in high risk patients. The study was approved by the ethics committees at all the hospitals.

Definitions

- Joint sepsis was defined as a positive culture from the joint at reoperation or a draining sinus.
- Strong evidence of joint sepsis was defined as four or more possible signs of sepsis present at follow-up (pain on weight-bearing and/or at rest, tenderness of the wound, fever, an X-ray with periostial reactions or progressive bone resorption, an increased erythrocyte sedimentation rate (20 mm above the preoperative value or > 35 mm), a posi-

tive joint aspiration, a positive arthrogram, a bone scan showing typical signs of infection or an increased C-reactive protein).

- Wound infection was simply defined as an area of erythema of more than one centimetre measured from the incision.
- Minor woundhealing problems were defined as an area of erythema of less than 1 cm measured from the incision, pus suture, small wound dehiscence, necrosis of the wound edge and blisters.
- Distant infections were diagnosed on the basis of positive cultures. In the urine, more than 10^5 bacteria/ml was defined as a positive culture. Blood cultures of *Staphylococcus epidermidis* were only regarded as positive if cultured twice or more. Only a few skin, pulmonary and other infections were diagnosed on a clinical basis.

Patients

A total of 3074 hip and 455 knee operations entered the trial, of which 278 hip and 58 knee operations were excluded. The most frequent reason for exclusion was the use of gentamicin-impregnated bone cement. From the remaining 2796 hip and 397 knee replacements, 145 and 35 were withdrawn, respectively. The major reasons were the administration of the wrong type and/or dose of antibiotics, death (not sepsis-related) within 7 days of the operation or a second operation within the same period of hospitalization. This left 2651 hip replacements (2547 patients) and 362 knee replacements (345 patients) for analysis. This series therefore represents a rather homogeneous group of patients who underwent replacements, from which a number of high risk patients were eliminated due to the use of gentamicin bone cement. The hip and knee replacements were analysed separately; the patient characteristics and trial results are shown in Table I.

The incidence of joint sepsis in hip replacements was 0.83% in the single dose group (95% confidence limits 0.33-1.32) and 0.45% in the three dose group (95% confidence limits 0.08-0.81). In the knee replacements, the incidence was 1.71% in the single dose group (95% confidence limits 0.09-3.33%) and 3.20% in the three dose group (95% confidence limits 0.63-5.77). These incidences are comparable with those reported in other large series on hip and knee replacements [8-13].

Table I Summary of patient characteristics and trial results

characteristics & results	HIP REPLACEMENT 1 dose n=1327	3 doses n=1324	total n=2651 (%)	KNEE REPLACEMENT 1 dose n=175	3 doses n=187	total n=362 (%)
mean age (years)	69 1	69 1	69 1	70 6	71 1	70 9
male/female	287/1040	266/1058	553/2098	23/152	23/164	46/316
DIAGNOSIS						
arthrosis	959	954	1913 (72 3)	100	83	183 (50 6)
rheumatoid arthr	83	77	160 (6 0)	41	51	92 (25 4)
fracture (fresh)	138	120	258 (9 7)	-	-	-
other	35	31	66 (2 5)	1	5	6 (2 7)
previous operations	112	142	254 (9 6)	33	47	80 (22 0)
joint sepsis	11	6	17 (0 6)	3$	6	9 (2 5)
wound infection	25	31	56 (2 1)	4	9	13 (3 6)
minor wound problems	169	166	335 (12 6)	33	35	68 (18 8)
haematoma (l/m/s)#	127/99/28	145/82/44	525 (20 0)	19/23/5	13/26/9	97 (26 8)
wound drainage	166	178	344 (13 0)	30	38	68 (18 8)
urinary tract infection	201	194	395 (14 9)	32	34	68 (18 8)
skin infection	31	26	57 (2 2)	2	4	6 (1 7)
pulmonary infection	18	20	38 (1 4)	3	5	8 (2 2)
septicaemia	5	4	9 (0 3)	-	2	2 (0 6)
bed days (mean)	26 3	24 0	25 2	32 1	30 0	31 0
total	34919 3	31863 2	66782 5	5623 5	5610 0	11233 5

(# = light/moderate/severe, $ = one other infection was diagnosed in a withdrawn patient who received three doses instead of a single dose)

Defined daily dose

To enable comparisons between the two groups of patients regarding their overall antibiotic drug use, the methodology of the Defined Daily Dose (DDD) was used[14]. The level of the DDD is based on the main indication for the drug and is expressed -where possible- as the weight of active substance. For each individual antibiotic drug, the total amount in grams was calculated and divided by its DDD value (depending on the route of administration) to give the total amount of DDDs. By adding the DDD values for the drugs, group DDDs and the total amount of DDDs was assessed. The DDD values were taken from the Nordic Statistics on Medicines[15].

DDD per 100 bed days

To make comparisons possible, the total value of DDDs was analysed in relation to the total number of bed days. For the hospitals, this relationship was expressed as DDD per 100 bed days. This unit provides a rough estimate of the proportion of patients that would receive antibiotic drug treatment. The total number of bed days was calculated from the data of individual patients. The number of bed days in hospital was missing in 45 patients and a correction was performed by adding the mean number of bed days from the patient group concerned for each missing value (Table I).

Results

Additional antibiotics

Additional antibiotics were prescribed in 20.7% of the hip replacements, versus 31.2% of the knee replacements. The percentage of patients on poly-therapy was also somewhat higher in the knee group than in the hip replacement group. There was no difference between the use of antibiotics in the single and three dose groups for either operation (Table II).

Table II Number of replacements with no therapy, mono therapy and poly-antibiotic therapy

	HIP REPLACEMENT						KNEE REPLACEMENT					
	1 dose	(%)	3 doses	(%)	total	(%)	1 dose	(%)	3 doses	(%)	total	(%)
no antibiotics	1047	(78 9)	1054	(79 6)	2101	(79 3)	123	(70 3)	126	(67 4)	249	(68 8)
mono-therapy	224	(16 9)	222	(16 8)	446	(16 8)	40	(22 9)	49	(26 2)	89	(24 6)
poly-therapy	56	(4 2)	48	(3 6)	104	(3 9)	12	(6 9)	12	(6 4)	24	(6 6)
Total	1327		1324		2651		175		187		362	

Indication for additional antibiotics

The amount of additional antibiotics, with the indication for which they were prescribed, is shown in Table III, expressed as DDD per 100 bed days. No large differences were observed between the single and three dose groups in hip and knee replacements.

The total amount of antibiotics prescribed was higher in the knee replacement group: nearly twice the amount of antibiotics were prescribed for wound problems and temperature e.c.i. The amount of antibiotics administered for distant infections in hip and knee replacement was fairly similar (around 6.5 DDD per 100 bed days). In the hip replacement group, the largest amount of antibiotics was administered for distant infections (53%) and somewhat less for wound problems (33%). In knee replacement, the amount of antibiotics administered for wound problems (44%) and distant infections (42%) was similar.

Table III Amount of additional antibiotics prescibed per indication in DDD per 100 bed days

	HIP REPLACEMENT			KNEE REPLACEMENT		
Indication antibiotics	1 dose n=1327 (%)	3 doses n=1324 (%)	total n=2651 (%)	1 dose n=175 (%)	3 doses n=187 (%)	total n=362 (%)
wound	3 56 (32 2)	3 81 (32 3)	3 77 (33 0)	6 88 (44 2)	6 94 (43 2)	6 91 (44 0)
distant infection	5 84 (52 9)	6 51 (55 1)	6 15 (53 9)	6 81 (43 8)	6 34 (39 5)	6 57 (41 8)
temperature e c i	1 19 (10 8)	1 12 (9 5)	1 15 (10 1)	1 76 (11 3)	2 50 (15 6)	2 12 (13 5)
other	0 47 (4 3)	0 18 (1 5)	0 33 (2 9)	0 11 (0 7)	0 12 (0 8)	0 13 (0 7)
totals	11 05 (100)	11 82 (100)	11 43 (100)	15 56 (100)	16 05 (100)	15 71 (100)

Duration of treatment

The length of antibiotic treatment in days is shown in Table IV. In hip replacement, no large differences were observed between the single and three dose groups although the number of patients in the single dose group with wound problems was somewhat higher than in hip replacement. The differences observed in the knee replacement group can be explained by the smaller number of patients and the large range of treatment days between the patients.
The overall length of antibiotic therapy for hip and knee replacement was fairly similar and depended mainly on the indication for antibiotic therapy and not on the type of operation. In this trial, orthopaedic surgeons prescribed antibiotics for wound problems for an average period of 18 days, for distant infections 10 days and for temperature e.c.i. 12 days.

Table IV Mean duration of additional antibiotic therapy per indication (in days) in combination with the number of patients receiving antibiotics (n)

Indication		HIP REPLACEMENT 1 dose n=1327	3 doses n=1324	total n=2651	KNEE REPLACEMENT 1 dose n=175	3 doses n=187	total n=362
wound	days	16 9	18 7	17 7	23 8	15 3	18 8
	(n)	(48)	(40)	(88)	(11)	(15)	(26)
distant infection	days	9 7	11 0	9 6	11 0	8 6	9 7
	(n)	(196)	(198)	(394)	(30)	(38)	(68)
temperature e c i	days	12 7	12 6	12 7	9 6	14 3	11 8
	(n)	(18)	(18)	(36)	(8)	(7)	(15)
other	days	3 3	2 3	3 0	1 0	1 0	1 0
	(n)	(35)	(24)	(59)	(7)	(5)	(12)

Types of antibiotic

In Table V, the DDD per 100 bed days for the several groups of antibiotics is shown. The antibiotics prescribed most often were (in descending order): the penicillin, the sulfonamides, the cephalosporines and nitrofurantoin. The only striking difference between the two types of operation was a higher DDD per 100 bed days for the penicillin group in knee replacements. Within the cephalosporin group, first generation cephalosporins, such as cefazolin, were prescribed in 85%, second generation cephalosporins in 14% and third generation in only 1%.

Table V Types of additional antibiotic prescibed in DDD per 100 bed days

Type of antibiotic	HIP REPLACEMENT 1 dose n=1327	3 doses n=1324	total n=2651	(%)	KNEE REPLACEMENT 1 dose n=175	3 doses n=187	total n=362	(%)
penicillin	4 767	5 115	4 931	(43 1)	7 499	7 747	7 890	(50 2)
sulfonamides	1 990	2 224	2 101	(18 4)	2 916	2 754	2 835	(18 0)
cefalosporins	1 787	1 958	1 873	(16 4)	1 095	2 060	1 582	(10 1)
nitrofurantoin	1 638	1 480	1 562	(13 7)	0 871	1 640	1 255	(8 0)
aminoglycosides	0 424	0 224	0 329	(2 9)	0 320	0 184	0 249	(1 6)
quinolones	0 136	0 260	0 199	(1 7)	0 402	0 378	0 381	(2 4)
tetracyclines	0 195	0 191	0 193	(1 7)	0 089	0 535	0 316	(2 0)
metronidazole	0 060	0 099	0 078	(0 7)	0 024	-	0 012	(0 1)
miconazols	0 014	0 024	0 021	(0 2)	-	-	-	-
erythromycine	0 043	0 220	0 013	(0 1)	-	0 285	0 142	(0 9)
isoniazid	-	0 020	0 010	(0 1)	-	-	-	-
lincosamides	-	-	-	-	0 551	0 281	0 416	(2 7)
fusidic acid	-	-	-	-	1 280	-	0 641	(4 1)
Total	11 05	11 82	11 43	(100)	15 56	16 05	15 71	(100)

Type of antibiotic and indication

More detailed information on the type of antibiotic prescribed for a particular indication, is presented in Table VI. Penicillins were the drug of choice for wound problems in both hip and knee replacement in more than two-thirds of the cases. Within this group, flucloxacillin was prescribed in 89%.
For distant infections (the majority being urinary tract infection -Table I), sulfonamides were the most popular (33-35%); the amount of nitrofurantoin (19-25%) and penicillin (25-28%) was fairly similar. For distant infections in the penicillin group, amoxycillin was prescribed in 54% and flucloxacillin in 29%.

Table VI Types of additional antibiotic prescribed for wound problems and distant infection in DDD per 100 bed days

	HIP REPLACEMENT				KNEE REPLACEMENT			
Type of antibiotic	wound problems	(%)	distant infecuon	(%)	wound problems	(%)	distant infection	(%)
sulfonamides	0 043	(1 2)	2 033	(33 0)	0 249	(3 6)	2 328	(35 4)
nitrofurantoin	-	-	1 550	(25 2)	-	-	1 255	(19 1)
penicillin	2 522	(66 7)	1 534	(24 9)	4 781	(69 2)	1 855	(28 2)
cephalosporins	0 885	(23 3)	0 527	(8 6)	0 356	(5 2)	0 595	(9 1)
tetracyclines	0 031	(0 8)	0 147	(2 4)	0 312	(4 5)	-	
quinolones	0 048	(1 3)	0 147	(2 4)	-	-	0 381	(5 8)
aminoglycosides	0 127	(3 4)	0 122	(2 0)	0 230	(3 5)	-	-
metronidazole	0 015	(0 4)	0 052	(0 8)	-	-	0 012	(0 2)
erythromicine	0 103	(2 7)	0 024	(0 4)	-	-	0 142	(2 7)
miconazole	-	-	0 015	(0 2)	-	-	-	-
lincosamides	-	-	-	-	0 320	(4 6)	-	-
isoniazid	-	-	-	-	-	-	-	-
fusidic acid	-	-	-	-	0 641	(9 3)	-	
Total	3 770	(100)	6 148	(100)	6 911	(100)	6 568	(100)

Discussion

Joint sepsis

In hip replacement, the difference in joint sepsis between the single and three dose group was 0.38% with an upper confidence limit of 0.90%. We could therefore not confirm that a single dose of cefuroxime was as equally effective as a three dose regimen[6]. The trial sample in the knee

replacement group was too small to draw definite conclusions[7]. A longer follow-up (with probably more cases of joint sepsis) is presently underway.

Use of additional antibiotics

In this study, data are presented on the use of additional antibiotics after a short course of perioperative prophylaxis, using a single dose or three doses of cefuroxime. In 20% of the hip and in 30% of the knee replacements, additional antimicrobial therapy was given. This use of antibiotics could partly be seen as a consequence of hospital-acquired infections. The prevalence of such infections varies widely between the hospitals (3.2% to 20%)[16].
Mono-therapy was employed in the majority of cases requiring antibiotic treatment. By using the DDD per 100 bed days methodology, it was possible to compare the use of antibiotics between groups. The analysis showed that the prescription of antibiotics was parallel in both groups and did not detect any difference per indication for antibiotic treatment. The use of antibiotics in knee replacement was higher than in hip replacement. This phenomenon can be explained by the higher incidence of postoperative wound problems and joint sepsis (Table I), as has also been found by several other authors[10-13]. Therefore, orthopaedic surgeons are inclined to administer antibiotics more often after knee replacement surgery, even for less serious woundhealing problems.
The duration of treatment for the different kinds of infection did not differ between the knee and the hip group. This confirms the idea that irrespective of the type of operation, wound problems and distant infections are treated in a similar way.

Wound infections were caused by the staphylococcus species in 51% of our patients[17]. It therefore seems worthwhile to choose a drug which covers these strains. For wound problems, penicillin and cephalosporins were prescribed for more than 60% of the cases (Table VI). Within the penicillin group, flucloxacillin was indeed chosen, as were the first generation cephalosporins, such as cefazolin. These drugs have broad coverage against staphylococci. Penicillin and cephalosporins were used mainly for wound infections.
For distant infections, mostly comprising urinary tract infections, sulfonamides in combination with trimethoprim were the drugs of choice. Nitrofurantoin was also popular. These drugs provide good coverage against the common causative microorganisms which can be found in these infections.

This study shows that using the DDD methodology, no relevant differences were found between a single dose and three doses of perioperative cefuroxime in hip and knee replacements, with respect to the amount, type, indication and duration of additional antibiotic therapy
The number of patients who received additional antibiotics was considerable and the main indications were distant infection (usually urinary tract infections) and woundhealing problems In the knee replacement group, more antibiotics were used than in the hip group, mainly for woundhealing problems.

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References

1 Dipiro J , Cheung R , Bowden T A , Mansberger J A , Single dose systemic antibiotic prophylaxis of surgical wound infection *Am J Surg 152* 552-559, 1986
2 Pollock A V , Surgical prophylaxis-the emerging picture *Lancet 1* 225-230, 1988
3 Heydemann J S , Nelson C L , Short-term preventive antibiotics *Clin Orthop 205* 184-187, 1986
4 Pollard J P , Hughes S P F , Scott J E , Evans M J , Benson M K D , Antibiotic prophylaxis in total hip replacement *Brit Med J 1* 707-709, 1979
5 Evrard J , Doyon F , Aacar J F , Salord J C , Mazas F , Flamant R , Two-day cefamandole versus five-day cephalzolin prophylaxis in 965 total hip replacements *Int Orthop 12* 69-73, 1988
6 Wymenga A B , van Horn J R , Theeuwes A , Muytjens H L , Slooff T J J H , Joint sepsis after infection prophylaxis with one or three doses of cefuroxime in 2651 hip replacements Submitted for publication
7 Wymenga A B , Van Horn J R , Theeuwes A , Muytjens H L , Slooff T J J H , Joint sepsis after infection prophylaxis with one or three doses of cefuroxime in 362 knee replacements Submitted for publication
8 Lidwell O M , Lowbury E J L , Whyte W , Blowers R , Stanley S J , Lowe D , Infection and sepsis after operation for total hip or knee-joint replacement influence of clean air, prophylactic antibiotics and other factors *J Hyg Camb 93* 505-529, 1984
9 Hill C , Mazas F , Flamant R , Evrard J , Prophylactic cefazolin versus placebo in total hip replacement *Lancet 1* 795-797, 1981
10 Johnson D P , Bannister G.C , The outcome of infected arthroplasty of the knee *J Bone and Joint Surg 68B* 795-803, 1986
11 Knutson K , Lindstrand A , Lidgren L , Survival of knee arthroplasties A nationwide multicentre investigation of 8000 cases *J Bone and Joint Surg 68B* 289-291, 1986
12 Grogan T J , Dorey F , Rollins J , Amstutz H C , Deep sepsis following total knee arthroplasty *J Bone and Joint Surg 68A* 226-234, 1986
13 Rand J A , Fitzgerald R H , Diagnosis and management of the infected total knee arthroplasty *Orthop Clin N Am 20* 201-210, 1989

14. Wertheimer A.I., The defined daily dose system DDD for drug utilization review. *Hosp. Pharm. 21*: 233-41, 258, 1986.
15. Anonymous. *Nordic statistics on medicines 1981-1983*. Part II. Nordic drug index with classification and defined daily doses. Uppsala: Nordic Council on Medicines, 1985.
16. Stahr Johansen K., Tikhomirov E., WHO Programme for the control of hospital infection. In: *Proceedings of the international symposium on control of hospital infection*, Rome, April 27-29, 1987.
17. Wymenga A.B., Van Horn J.R., Theeuwes A., Muytjens H.L., Slooff T.J.J.H., The relation of wound, urine cultures and joint sepsis after hip and knee replacement. Submitted for publication.

Chapter IX
Summary

Joint sepsis after prosthesis implantation still is one of the most severe complications after replacement surgery, although the incidence has fallen from 10% to 1-3% during the past decades. A review of the current literature (chapter II) revealed that most prosthesis-related infections are initiated during operation by contamination with bacteria-carrying particles from the air as a result of dispersion of skin scales from individuals in the operating room. A small number of infections is caused by hematogenous seeding of bacteria. Glycocalyx, a slime layer produced by bacteria, plays an important role in the pathogenesis of infections, especially in the presence of biomaterial.
Clean-air systems in combination with perioperative systemic antibiotics reduce prosthesis-related infections from 3 or 4 per cent to a few per thousand. The use of antibiotic-loaded bone cement is advised in high risk patients although further evaluation is needed.
Physical examination of the patient, laboratory tests such as the E.S.R. and C-reactive protein, serial radiograms, isotope scanning techniques and joint aspiration can all help diagnose prosthesis-related infection. However a definitive diagnosis is possible only by culturing several samples of material obtained from the interface during revision operation. A perioperative frozen section of interface tissue showing acute (more than 5 leucocytes per field, 500 x) or severe chronic inflammation (more than 50 lymphocytes) is higly suggestive of sepsis.

A single perioperative antibiotic dose is increasingly used in orthopaedic surgery and since there were no studies available about the efficacy of a single dose prophylaxis in joint replacement we performed a randomized controlled trial, stratified for hip and knee replacement. The experimental arm recieved one dose of cefuroxime and the control group received three doses (24 hours). All operations were performed in conventionally ventilated operating rooms. Hip and knee replacements were separately analysed after the trial because patient characteristics and incidence of joint sepsis differed considerably in both groups.

In chapter III, 2651 hip replacements were analyzed, 1327 patients recieved a single dose and 1324 patients three doses of cefuroxime. There were no differences between the incidence of postoperative woundhealing problems, urinary tract and other distant infections in the one and three dose group and the usage of antibiotics after prophylaxis did not differ either.
After a mean follow-up of 13 months, joint sepsis was diagnosed in 17 patients (0.64%); 11 in the one dose group (0.83%, 95% confidence limits 0.33 - 1.32%) and in 6 in the three dose group (0.45%, 95% confidence limits 0.08 - 0.81%). This difference is not significant (one tailed chi-square test, $p > 0.05$). The estimated difference between the one and three dose group was 0.38% (95% confidence limits 0-0.9%).
The equal efficacy of the one dose cefuroxime compared with the three dose regimen could, with these low numbers of joint sepsis not be confirmed. An extended follow-up, with probably more cases of joint sepsis diagnosed, may provide more conclusive data and a three dose regimen is recommended untill further data become available.

The trial results of the knee cohort were reported in chapter IV. 362 operations were analysed, 175 in the one dose group and 187 in the three dose group. There were no differences between the incidences of hematoma and minor postoperative woundhealing problems but there were more woundinfections in the three dose group. There were also no differences between the groups with respect to urinary tract and other distant infections and antibiotic usage after prophylaxis.
After a mean follow-up of 12 months joint sepsis was diagnosed in 9 patients (2.45%). Three cases were identified after 175 operations in the one dose group (1.7%, 95% confidence limits 0.09-3.33%) and in 6 after 187 operations in the three dose group (3.2%, 95% confidence limits 0.63-5.77%). This difference is not significant (one tailed chi-square test, $p > 0.05$). The numbers of the operations were too small to draw definitive conclusions about the equal efficacy of the single dose in large numbers of operations.

With the prospective data of the dose-defining studies, we were able to identify a number of independent acting riskfactors, associated with joint sepsis after hip and knee replacement.

In hip replacement (chapter V) the risk ratio (RR) for joint sepsis was increased in patients with diabetes (RR=3.7), failed fracture treatment (RR=5.4), and a break in sterility during operation (RR=3.4). Patients with a woundinfection were 62.2 times more at risk.
Patients from whom a woundculture or bloodculture was taken were 11.6

and 7.3 times more at risk, patients with a positive urine culture 4.9 times, respectively. Also at risk for joint sepsis were patients who left the hospital with an unhealed wound at hospital discharge (RR=22.2) or after a difficult and prolonged reconvalescence period (RR=5.2). A reoperation for mechanical complications was another major riskfactor; 4 out of 64 patients developed joint sepsis after this second operation (RR=9.5).
Gentamicin bone cement is recommended in high risk patients in order to reduce the incidence of joint sepsis. Diabetes patients should be monitored carefully. Woundinfection is an indication for antibiotic therapy, guided by woundculture results and surgical evacuation of a draining hematoma in the presence of woundinfection is mandatory. Minor woundhealing problems do not form an indication for antibiotic therapy. Patients who are discharged from the hospital with an unhealed wound or after a difficult reconvalescence period should recieve adjuntive outpatient care.

Riskfactors associated with joint sepsis in knee replacement were described in chapter VI. Reumatoid arthritis was the most important riskfactor (RR=5.0) that was identified in the pre- and peroperative period.
When patients developed a woundinfection or had antibiotics prescribed for woundproblems, they ran a very high risk for joint sepsis (RR=17.2 and 20.8). The risk was also increased in the presence skin necrosis (RR=14.7) and wound dehiscence (RR=4.5) especially in combination with another woundhealing problem such as erythema or drainage. An increased risk was also found in patients from whom a woundculture (RR=10.7) or bloodculture (RR=3.9) was taken and in patients who left hospital with an unhealed wound (RR=20.3) or with a painfull and limited knee function (RR=7.0). Reoperation after the index arthroplasty was another important risk factor since 3 additional patients of 24 (12.5%) developed joint sepsis after reoperation (RR=4.7).
The use of gentamicin bone cement might be beneficial for high risk patients with reumatoid arthritis (and probably also diabetes and previous surgery), and perhaps also for knee patients without riskfactors since the infection rate is approximatly fourfold that of the hip replacements. Further trials are needed to evaluate this. Patients with high risk woundproblems should receive adequate antibiotic therapy. This is not indicated in the presence of a single minor woundproblem, hematoma or drainage. Significant skin defects should be closed. Patients, discharged with an unhealed wound or painfull limited knee function should undergo frequent outpatient visits.

The relation of wound and urine cultures and later joint sepsis after replacement surgery was analysed in chapter VII. In 26 patients with

joint sepsis (17 hip replacements and 9 knee replacements) *S. aureus* (42%), *S. epidermidis* (12%), gram-negative bacteria (24%) and anaerobics (4%) were identified as causative agents and cefuroxime adequately covered this spectrum.
Later joint sepsis was preceded by woundinfection in 12 of 26 patients. When *S.aureus* was cultured from the wound after hip replacement in the postoperative period the risk of joint sepsis was 24 times increased, with gram-negative bacteria 17 times and with other species 10 times, when compared with patients without a woundculture. *S. epidermidis* was not related to joint sepsis. In knee replacement *S. aureus* and *S. epidermidis* were not related to joint sepsis, but isolation of gram-negative and other organisms increased the risk 17 and 15 times, respectively.
Perioperative joint cultures were positive in 26 out of 622 (4.2%) cases but not one of the 26 patients with a positive culture developed later joint sepsis. Joint sepsis was related to the 140 of 939 (15%) positive vacuum-drain cultures, but the woundculture was more reliable in predicting the risk of joint sepsis and the eventual causative agent. Perioperative joint cultures and postoperative draincultures are therefore not indicated in primary joint replacement.
Postoperative urinary tract infection occurred in 15% of the patients and was related to urinary catheters and the period the catheter was in situ. There was an increased risk for joint sepsis in the presence of a primary tract-infection, but this could not be explained by early postoperative hematogenous bacterial seeding to the joint. Five patients developed septicaemia with a catheter in situ more than 72 hours and removal is recommended before the third day.

The use of additional antibiotics, prescribed after the routine cefuroxime prophylaxis is described in chapter VII. No relevant differences were observed, between the groups with a single dose or three doses perioperative cefuroxime with respect to the total amount, type, indication and duration of therapy of the prescribed additional antibiotics. The amount of antibiotics was expressed in 'Defined Daily Doses' (DDD).
Additional antibiotics were used in 21% of patients after hip and 31% after knee replacement. In total 11.4 DDD per 100 bed days of antibiotics were prescribed in hip replacement and 15.7 DDD per 100 bed days in knee replacement. For woundproblems 3.8 and 6.9 DDD per 100 bed days were given in respectively hip and knee replacement. For distant infections, such as in the urinary tract, 6.5 DDD per 100 bed days were administered in both the hip and the knee group. Duration of antibiotic therapy varied only with indication. Most often prescribed were penicillins (43-50%), sulfonamides (18%), cefalosporines (10-16%)

and nitrofurantoine (8-13%), and drug use was related to the kind of infections.

In this study the efficacy of a single perioperative dose of cefuroxime was evaluated in hip and knee replacement surgery, using a three dose regimen as control. The incidence of joint sepsis in hip replacement was 0.64% and in knee replacement 2.45%, respectively.
No significant differences were found between the one dose group and the three dose group with respect to postoperative woundproblems, distant infections and usage of antibiotics after prophylaxis.
The equal efficacy of the single perioperative dose cefuroxime, compared with the three dose regimen, could not be confirmed due to the low numbers of joint sepsis. A longer follow-up period, with probably more cases of joint sepsis diagnosed, may provide more conclusive data.
We were able to identify a number of important riskfactors for joint sepsis from the prospective data of the dose defining study. Instigation of additional prophylactic and/or therapeutic treatment is advised in high risk patients, in order to reduce the incidence of joint sepsis.

Chapter X
Samenvatting

Prothese-infectie blijft, ondanks een afname van de incidentie in de laatste decaden van 10% tot 1 à 3%, één van de meest gevreesde complicaties na gewrichtsvervanging met een endoprothese. In hoofdstuk II blijkt uit een overzicht van de recente literatuur, dat de meeste prothese-gerelateerde infecties ontstaan tijdens de operatie door contaminatie met bacterie dragende deeltjes vanuit de lucht. Deze luchtcontaminatie ontstaat door het strooien van huidschilfers door personen in de operatiekamer. Een klein deel van de infecties ontstaat door hematogene uitzaaing van bacterien. Glycocalyx, een slijmlaag die geproduceerd wordt door bacterien, speelt een grote rol in de pathogenese van infecties, vooral in aanwezigheid van biomaterialen.
Schone-lucht systemen in combinatie met perioperatieve systemische antibiotica reduceren het aantal prothese infecties tot enkele per duizend. Het gebruik van antibiotica-houdend botcement wordt geadviseerd bij risico-patienten, maar verdere evaluatie van dit cement is nodig.
Lichamelijk onderzoek van de patient, laboratoriumtesten zoals de bezinking en het C-reactieve proteine, seriele rontgenfoto's, isotopen scans en gewrichts-aspiraties kunnen waardevol zijn bij het stellen van de diagnose van prothese-gerelateerde infecties, maar leveren nooit het definitieve bewijs voor infectie. De uiteindelijk diagnose kan slechts verkregen worden uit meerdere biopsie-kweken van de interface gedurende de revisie operatie. Een peroperatieve vriescoupe van interface met acute ontsteking (meer dan 5 leucocyten per veld, 500x) of ernstige chronische ontsteking (meer dan 50 lymfocyten) is sterk suggestief voor infectie.

De éénmalige perioperatieve antibiotica prophylaxe wordt in toenemende mate toegepast in de orthopaedie. Omdat er geen studies bekend waren over de effectiviteit van de éénmalige dosis prophylaxe bij gewrichtsvervangende operaties is een prospectieve gerandomiseerde studie verricht, waarin heup- en knie-arthroplastieken werden gestratificeerd. Patienten in de experimentele arm ontvingen een éénmalige

dosis cefuroxim en de controle groep een driemalige dosis (24 uur). Alle operaties werden uitgevoerd in zogenaamde conventioneel geventileerde operatiekamers. De heup- en knieprothesen werden na de trial apart geanalyseerd omdat bleek dat het patientenmateriaal en de incidentie van diepe infectie duidelijk verschilde tussen deze groepen.

In hoofdstuk III werden de resultaten van 2651 heupvervangingen geanalyseerd, waarvan 1327 in de één dosis groep en 1324 in de drie dosis groep. De groepen waren goed vergelijkbaar.
Er werden tussen de één en drie dosis groep geen verschillen gevonden met betrekking tot postoperatieve wondstoornissen, urineweginfecties, andere infecties op afstand en het gebruik van antibiotica na de prophylaxe.
Na een gemiddelde follow-up van 13 maanden werd bij 17 patienten (0.64%) diepe infectie vastgesteld; bij 11 in de één dosis groep (0.83%, 95% betrouwbaarheidsinterval 0.33-1.32%) en bij 6 in de drie dosis groep (0.45%, 95% betrouwbaarheidsinterval 0.08-0.81%). Dit verschil is niet significant (eenzijdige chi-kwadraat toets, $p > 0.05$).
Het geschatte verschil tussen de beide dosis groepen was 0.38% (95% betrouwbaarheidsinterval 0-0.9%). De gelijkwaardige effectiviteit van de éénmalige dosis cefuroxim, in vergelijking met de drie dosis prophylaxe, kan daarom nog niet worden bevestigd. De huidige aantallen diepe infectie zijn te klein om definitieve conclusies te trekken. Een langere follow-up met waarschijnlijk meer diepe infecties kan mogelijk meer duidelijk verschaffen. Vooralsnog wordt een driemalige dosis geadviseerd.

Hoofdstuk IV beschrijft de resultaten van de trial voor 362 totale knie operaties, waarvan 175 plaatsvonden met een één dosis prophylaxe en 187 met een drie dosis prophylaxe. De groepen waren goed vergelijkbaar. Er werden tussen de één en drie dosis groep geen verschillen gevonden met betrekking tot 'kleine' postoperatieve wondstoornissen, urineweginfectie, andere infecties op afstand en het gebruik van antibiotica na de prophylaxe. Wel waren er meer wondinfecties in de drie dosis groep.
Na een gemiddelde follow-up van 12 maanden werd bij 9 patienten (2.45%) diepe infectie vastgesteld; bij drie in de één dosis groep (1.71%, 95% betrouwbaarheidsinterval 0.09-3.33%) en bij 6 in de drie dosis groep (3.2%, 95% betrouwbaarheidsinterval 0.63-5.77%). Dit verschil is niet significant (eenzijdige chi-kwadraat toets, $p > 0.05$). De steekproef voor de kniegroep is te klein om definitieve uitspraken te doen over de gelijkwaardige effectiviteit van de éénmalige dosis.

Met behulp van de prospectief verzamelde gegevens uit de dosis studie waren wij in staat om een analyse uit te voeren naar risicofactoren voor diepe infectie bij heup- en knie-arthroplastieken.

Bij analyse van de heup-arthroplastieken (hoofdstuk V) bleek dat patienten met diabetes, mislukte fractuur osteosynthese en steriliteitsonderbreking tijdens de operatie, respectievelijk 3.7 , 5.4 en 3.4 maal zoveel kans op infectie hadden dan patienten zonder deze factoren.
In de postoperatieve periode gaf wondinfectie zelfs 62.2 maal meer kans op diepe infectie. Patienten van wie een wond- of bloedkweek werd genomen, hadden 11.6 en 7.3 maal meer kans en patienten met een positieve postoperatieve urinekweek hadden 4.9 maal meer kans op diepe infectie. Wanneer een patient het ziekenhuis verliet met een niet-genezen wond of na een moeilijke revalidatieperiode was het risico 22.2 en 5.2 maal verhoogd. Reoperatie in verband met mechanische problemen was ook een belangijke risicofactor; 4 van 64 patienten ontwikkelden nog diepe infectie na deze tweede operatie (9.5 maal meer kans).
Voor patienten met een verhoogd risico wordt het gebruik van gentamicine botcement aanbevolen als extra prophylaxe tegen infectie. Patienten met diabetes dienen perioperatief goed ingesteld te worden. Wondinfectie is een indicatie voor antibiotische therapie, op geleide van de wondkweek. Bij wondstoornissen zonder wondinfectie is antibiotische therapie niet geindiceerd. Bij patienten met wondinfectie en een drainerend hematoom is chirurgische evacuatie van het hematoom aangewezen. Patienten die het ziekenhuis verlaten met een niet-genezen wond of na een moeilijke revalidatieperiode dienen extra poliklinische zorg te ontvangen.

Bij de analyse van de knie-arthroplastieken (hoofdstuk VI) bleek dat reumatoide arthritis de belangrijkste risicofactor was voor diepe infectie in de pre- en peroperatieve periode, die resulteerde in een 5.0 maal verhoogde kans.
Patienten met een wondinfectie en patienten die antibiotica kregen in verband met wondproblemen hadden een 17.2 en 20.8 maal verhoogde kans op diepe infectie. Het risico was ook duidelijk verhoogd bij wondrandnecrose (14.7 maal) en wonddehiscentie (4.5 maal), vooral in combinatie met andere wondstoornissen zoals roodheid en drainage. Er was ook een verhoogd risico voor patienten van wie wondkweken (10.7 maal) of bloedkweken (3.9 maal) werden genomen en voor patienten met een niet-genezen wond (20.3 maal) of een pijnlijke en in functie beperkte knie (7.0 maal) bij ontslag uit het ziekenhuis. Daarnaast was reoperatie in verband met mechanische problemen ook een belangrijke

risicofactor; 3 van 24 patienten ontwikkelden nog diepe infectie na deze tweede operatie (4.7 maal verhoogde kans).
Het gebruik van gentamicine botcement zou het aantal infecties bij risico patienten met reumatoide arthritis (en waarschijnlijk ook met diabetes en eerdere operaties) kunnen reduceren. Het dient zelfs overwogen te worden bij patienten zonder risicofactoren, omdat de diepe infectie incidentie vier keer zo hoog is als bij heup-arthroplastieken uitgevoerd in dezelfde ziekenhuizen. Verdere trials met gentamicine botcement zijn nodig om dit te onderzoeken.
Naast wondinfectie is ook wondrandnecrose en wondranddehiscentie in combinatie met andere wondstoornissen een indicatie voor antibiotische therapie. Bij een enkelvoudige wondstoornis, hematoom of drainage is antibiotische therapie niet geindiceerd. Grotere huiddefecten moeten gesloten worden om diepe infectie te voorkomen. Patienten die het ziekenhuis verlaten met een niet-genezen wond of een pijnlijke en in functie beperkte knie dienen nauwkeurig gevolgd te worden.

De relatie van wond- en urinekweken met latere diepe infectie bij de heup- en knie-arthroplastiek werd in hoofdstuk VII geanalyseerd. Bij 26 patienten met diepe infectie werden *S. aureus* (42%), *S. epidermidis* (12%), gram-negatieven (24%) en anaerobe bacterien (4%) als verwekkers gekweekt en cefuroxim dekte dit spectrum goed.
Diepe infectie werd bij 12 van de 26 patienten door postoperatieve wondinfectie voorafgegaan. Als bij de heup-arthroplastiek *S. aureus* werd gekweekt van de postoperatieve wond dan was de kans op diepe infectie 24 keer verhoogd, bij gram-negatieven 17 keer en bij andere bacterien 10 keer, in vergelijking met patienten zonder wondkweken. Er was geen verband met *S. epidermidis*. Bij de knie-arthroplastiek was geen relatie met *S. aureus* en *S. epidermidis*, maar na isolatie van gram-negatieve of andere micro-organismen was de kans op diepe infectie respectievelijk 17 en 15 maal verhoogd.
Peroperatieve gewrichtskweken waren bij 26 van de 622 (4.2%) patienten positief, maar niet één patient met een positieve kweek ontwikkelde diepe infectie. Diepe infectie was wel gerelateerd aan positieve drainkweken (140 van 939, 15%), maar de wondkweek bleek betrouwbaarder in het voorspellen van de kans op diepe infectie en een eventuele verwekker van diepe infectie. Peroperative gewrichtskweken en drainkweken behoeven daarom niet routinematig verricht te worden bij primaire arthroplasticken.
Postoperatieve urineweg infecties kwamen voor bij 15% van de patienten en er was een duidelijke relatie met urinecatheters en ook met de duur van cathetergebruik. Bij heup-arthroplastieken bestond een positieve relatie tussen postoperatieve urineweg infecties en diepe infectie,

maar dit kon niet door vroeg postoperatieve hematogene uitzaaiing verklaard worden. Omdat bij vijf patienten urosepsis ontstond nadat een urinecatheter langer dan 72 uur in situ was, wordt verwijdering van de catheter voor de derde dag aanbevolen.

Het gebruik van antibiotica na de routinematige cefuroxim prophylaxe, werd in hoofdstuk VII beschreven. Er was geen belangrijk verschil tussen de één en drie dosis groep met betrekking tot de hoeveelheid, het type, de indicatie en de duur van de gebruikte antibiotica. De hoeveelheid antibioticum werd uitgedrukt in zogenaamde 'Defined Daily Doses' (DDD).
Additionele antibiotica werden gebruikt in 21% van de patienten na een heup-arthroplastiek en in 31% na een knie-arthroplastiek. In totaal werden 11.4 DDD's per 100 bed dagen antibioticum gegeven na een heuparthroplastiek en 15.7 DDD's per 100 bed dagen na een knie-arthroplastiek. Voor wondproblemen werden respectievelijk 3.8 en 6.9 DDD's per 100 bed dagen antibioticum toegediend na een heup- en knie-arthroplastiek. Voor infectie op afstand werden 6.5 DDD's per 100 bed dagen antibioticum voorgeschreven na beide operaties. De duur van de therapie varieerde alleen met de indicatie.
Penicillines (43-50%), sulfonamides (18%), cefalosporines (10-16%) en nitrofurantoine (8-13%) werden het meest voorgeschreven en het antibioticum gebruik was gerelateerd aan het type infectie.

In deze studie werd de effectiviteit van een éénmalige perioperatieve dosis cefuroxim onderzocht bij heup- en knie-arthroplastieken, met een driemalige dosering als controle. De incidentie van diepe infectie bij heup-arthroplastieken was 0.64% en bij knie-arthroplastieken 2.45%.
Er werden geen significante verschillen gevonden tussen de één dosis groep en de drie dosis groep met betrekking tot wondinfecties, wondstoornissen, infecties op afstand en het gebruik van antibiotica na de prophylaxe.
De gelijkwaardige effectiviteit van de éénmalige perioperatieve dosis cefuroxim in vergelijking met de driemalige dosering, kon niet bevestigd worden door het lage aantal patienten met diepe infectie. Een langere follow-up periode, waarin waarschijnlijk nog meer patiënten met diepe infectie gevonden zullen worden, kan in de toekomst meer duidelijkheid verschaffen.
Met de prospectief verzamelde gegevens uit de dosis studie was het mogelijk om een aantal belangrijke risicofactoren voor diepe infectie te identificeren. Extra prophylactische en/of therapeutische maatregelen worden aanbevolen voor patienten met risicofactoren om de infectie incidentie te reduceren.

Supplement Ia: General summary of the data of the dose-defining study on hip replacement

	1 dose	3 doses	total	(%)
ENTRY, EXCLUSIONS, WITHDRAWALS				
exclusions	141	137	278	9 04
inclusions	1399	1397	2796	
withdrawals	72	73	145	5 19
ANALYSED	1327	1324	2651	
Hospital stay (days)				
preoperative	3 5	2 7	-	
overall	26 3	24 1	-	
PREOPERATIVE DATA hip				
Age (years)				
0-50	66	62	128	4 83
51-60	178	178	356	13 43
61-70	421	439	860	32 44
71-80	502	487	989	37 31
>81	160	158	318	12 00
Sex				
male	287	266	553	20 86
female	1040	1058	2098	79 14
Quetelet index (kg/m^2)				
missing	216	220	436	16 45
<25	422	418	840	31 69
25-30	526	507	1033	38 97
>=30	163	179	342	12 90
Physical condition				
good	1102	1123	2225	83 93
moderate	206	184	390	14 71
poor	19	17	36	1 36

	1 dose	3 doses	total	(%)
Concurrent diseases:				
cns	58	54	112	4.22
cardiovascular	191	171	362	13.66
respiratory tract	86	87	173	6.53
gastro-intestinal	29	26	55	2.07
diabetes	42	58	100	3.77
rheumatoid arthritis	90	83	173	6.53
prostatism	15	5	20	0.75
prolaps/pessarium	6	7	13	0.49
other	129	121	250	9.34
Preoperative infections:				
pulmonary	9	8	17	0.64
skin	13	20	33	1.24
other	13	8	21	0.79
Use of steroids:	36	33	69	2.60
Type of arthroplasty:				
hemiarthroplasty	86	81	167	6.30
total hip	1241	1243	2484	93.70
Type of surgery:				
primary	1301	1284	2585	97.51
revision	26	40	66	2.49
Side:				
left	649	611	1260	47.53
right	678	713	1391	52.47
Diagnosis hip:				
idiopathic arthrosis	919	934	1853	69.90
post-traumatic arthrosis	14	7	21	0.79
secondary arthrosis	91	106	197	7.43
rheumatoid arthritis	88	80	168	6.34
fracture	176	158	334	12.60
other	39	39	78	2.94
Previous operations hip:				
osteotomy	42	56	98	3.70
prosthesis	26	40	66	2.49
osteosynthesis fracture	33	30	63	2.38
other	11	16	27	1.02

	1 dose	3 doses	total	(%)
PEROPERATIVE DATA hip				
Surgeon:				
staff	1245	1242	2487	93.81
resident	82	82	164	6.19
Acetabular prosthesis:				
no	89	86	175	6.60
cemented	874	877	1751	66.05
cementless	364	361	725	27.35
Femoral prosthesis:				
cemented	1117	1099	2216	83.59
cementless	210	225	435	16.41
Approach hip:				
(antero)lateral	439	422	861	32.48
posterolateral	888	902	1790	67.52
Degree of difficulty operation:				
normal	1112	1090	2202	83.06
difficult	196	206	402	15.16
very difficult	19	28	47	1.77
Breakdown of sterility:	75	82	157	5.92
Duration of operation (minutes):				
missing	28	18	46	1.74
< 60	360	352	712	26.86
60-120	807	811	1618	61.03
120-180	125	134	259	9.77
>180	7	9	16	0.60
Blood loss (ml):				
missing	55	37	92	3.47
< 500	609	625	1234	46.55
500-1000	481	462	943	35.57
1000-1500	128	133	261	9.85
>1500	554	67	121	4.56
Drains used:				
missing	3	4	7	0.26
1	68	62	130	4.90
2	959	981	1940	73.18
3 or 4	297	277	574	21.65

	1 dose	3 doses	total	(%)
Wound rinse:				
no	989	1009	1998	75.37
povidone iodine	110	104	214	8.07
ab-solution	228	211	439	16.56
POSTOPERATIVE DATA hip				
Haematoma:				
light	127	145	272	10.26
moderate	99	82	181	6.83
severe	28	44	72	2.72
Minor woundhealing problems:	169	166	335	12.64
erythema <= 1 cm	133	116	249	9.39
pus suture	15	15	30	1.13
dehiscence	12	27	39	1.47
blister	21	24	45	1.70
wound edge necrosis	2	0	2	0.08
Wound drainage:				
serous	141	154	295	11.13
purulent	10	10	20	0.75
blood	15	14	29	1.09
Drainage drain wound:				
serous	185	185	370	13.96
purulent	2	2	4	0.15
Wound infection (erythema > 1 cm):	25	31	56	2.11
Urine catheter (intermittent):				
once	120	112	232	8.75
twice	44	45	89	3.36
3 times or more	34	42	76	2.87
Urine catheter a demeure:				
< 24 hours	118	102	220	8.30
24-48 hours	191	242	433	16.33
24-72 hours	94	75	169	6.37
> 72 hours	184	177	361	13.62
Drain fluid production:				
< 250 ml	203	191	394	14.86
250-500 ml	556	548	1104	41.64
500-750 ml	303	333	636	23.99
> 750 ml	224	206	430	16.22

	1 dose	3 doses	total	(%)
Day drain removal:				
1-3rd day	1175	1168	2343	88.38
4th day	93	80	173	6.53
5th day	37	40	77	2.90
> 5th day	22	36	58	2.19
Anticoagulation medication:				
coumarine	839	844	1683	63.49
coumarine + heparin	362	384	746	28.14
coumarine + (reo)macrodex	73	65	138	5.21
other	53	31	84	3.17
Situation at discharge:				
wound not healed	15	23	38	1.43
temperature elevated	17	12	29	1.09
painful/limited function	53	42	95	3.58
difficult reconvalescence	101	71	172	6.49
Preoperative sediment (> 5 leucos):				
no	830	860	1690	63.75
yes	187	171	358	13.50
COMPLICATIONS:				
orthopaedic (conservative)	48	46	94	3.55
reoperation mechanical	16	7	23	0.87
general complication clean	33	32	65	2.45
general complication not clean	14	13	27	1.02
invasive diagnostics	12	5	17	0.64
clean general surgery	13	4	17	0.64
not clean surgery	6	3	9	0.34
other elective surgery	15	15	30	1.13
death in hospital	11	5	16	0.60
CULTURES hip				
Wound cultures:				
positive	42	48	90	3.39
negative	35	30	65	2.45
Operative cultures:				
positive	11	14	25	0.94
negative	255	265	520	19.62
Drain culture:				
positive	65	57	122	4.60
negative	340	344	684	25.80

	1 dose	3 doses	total	(%)
Urine preoperative:				
positive	29	32	61	2.30
clinical diagnosis	2	0	2	0.08
negative	114	129	243	9.17
Urine postoperative:				
positive	198	191	389	14.67
clinical diagnosis	3	3	6	0.23
negative	142	132	274	10.34
Pulmonary tract:				
positive	11	13	24	0.91
clinical diagnosis	7	7	14	0.53
negative	9	10	19	0.72
Skin:				
positive	12	8	20	0.75
clinical diagnosis	19	18	37	1.40
Blood:				
positive	5	4	9	0.34
negative	42	30	72	2.72
Other:				
positive	2	2	4	0.15
clinical diagnosis	4	1	5	0.19
negative	2	0	2	0.08
ADDITIONAL ANTIBIOTICS (POSTOPERATIVE) hip				
Wound	48	40	88	3.32
Urine preoperative	21	20	41	1.55
Urine postoperative	158	155	313	11.81
Pulmonary tract	8	16	24	0.91
Skin	6	8	14	0.53
Other infections	7	5	12	0.45
Temperature eci	18	18	36	1.36
Other reasons	35	23	58	2.19
FOLLOW-UP hip				
Mean follow-up (days)	414	421	-	
Mechanical reoperations	33	31	64	2.41
(Joint sepsis after reoperation	3	1	4	0.15)
Joint sepsis	11	6	17	0.64

Supplement Ib: General summary of the data of the dose-defining study on knee replacement

	1 dose	3 doses	total	(%)
ENTRY, EXCLUSIONS, WITHDRAWALS:				
exclusions	33	25	58	12.7
inclusions	192	205	397	-
withdrawals	17	18	35	8.8
ANALYSED	175	187	362	
Hospital stay (days):				
preoperative	3.15	4.07	-	
overall	32.13	30.0	-	
PREOPERATIVE DATA knee				
Age (years):				
0-50	6	7	13	3.59
51-60	15	18	33	9.12
61-70	55	55	110	30.39
71-80	77	88	165	45.58
>80	22	19	41	11.33
Sex:				
male	23	23	46	12.71
female	152	164	316	87.29
Quetelet index (kg/m2):				
missing	27	28	55	15.19
<25	51	51	102	28.18
25-30	58	61	119	32.87
>=30	39	47	86	23.76
Physical condition:				
good	139	148	287	79.28
moderate	36	38	74	20.44
poor	0	1	1	0.28

	1 dose	3 doses	total	(%)
Concurrent diseases:				
cns	2	3	5	1.38
cardiovascular	9	24	33	9.12
respiratory tract	6	6	12	3.31
gastro-intestinal	5	2	7	1.93
diabetes	9	8	17	4.70
rheumatoid arthritis	53	55	108	29.83
prostatism	1	1	2	0.55
prolaps/pessarium	1	2	3	0.83
other	7	13	20	5.52
Preoperative infections:				
pulmonary	0	2	2	0.55
skin	1	1	2	0.55
other	0	2	2	0.55
Use of steroids:	17	17	34	9.39
Type of surgery:				
primary	173	182	355	98.07
revision	2	5	7	1.93
Side:				
left	80	89	169	46.69
right	95	98	193	53.31
Diagnosis knee:				
idiopathic arthrosis	118	117	235	64.92
post-traumatic arthrosis	4	9	13	3.59
rheumatoid arthritis	52	55	107	29.56
other	1	6	7	1.93
Previous operations knee:				
arthrotomy	8	14	22	6.08
osteotomy	8	16	24	6.63
prosthesis	2	5	7	1.93
menisectomy	3	6	9	2.49
other	12	6	18	4.97
PERIOPERATIVE DATA knee				
Surgeon:				
staff	167	177	344	95.03
resident	8	10	18	4.97

	1 dose	3 doses	total	(%)
Type of fixation knee prosthesis:				
cemented	133	142	275	75.97
non-cemented	42	45	87	24.03
Type of prosthesis knee:				
non-constrained	145	148	293	80.94
semi-constrained	30	39	69	19.06
Degree of difficulty operation:				
normal	149	151	300	82.87
difficult	23	33	56	15.47
very difficult	3	3	6	1.66
Breakdown of sterility:	5	10	15	4.14
Duration of operation:				
missing	3	0	3	0.83
<60	12	13	25	6.91
61-120	133	133	266	73.48
121-180	26	39	65	17.96
>180	1	2	3	0.83
Blood loss (ml):				
missing	89	81	170	46.96
< 500	72	97	169	46.69
500-1000	11	8	19	5.25
1000-1500	2	0	2	0.55
>1500	1	1	2	0.55
Drains used:				
1	32	26	58	16.02
2	121	135	56	70.72
3 or 4	22	26	46	13.26
Wound rinse:				
no	139	152	291	80.39
povidone iodine	18	17	35	9.67
ab-solution	18	18	36	9.94
POSTOPERATIVE DATA knee				
Haematoma:				
light	19	13	32	8.84
moderate	23	26	49	13.54
severe	5	9	14	3.87

	1 dose	3 doses	total	(%)
Minor woundhealing problems:	33	35	68	18.78
erythema <= 1 cm	16	19	35	9.67
pus suture	0	2	2	0.55
dehiscence	12	14	26	7.18
blister	2	1	3	0.83
wound edge necrosis	6	6	12	3.31
Wound drainage:				
serous	23	28	51	14.09
purulent	1	3	4	1.10
blood	6	7	13	3.59
Drainage drain wound (serous):	6	5	11	3.04
Wound infection (erythema > 1 cm):	4	9	13	3.59
Urine catheter (intermittent):				
once	7	9	16	4.42
twice	4	3	7	1.93
3 times or more	1	5	6	1.66
Urine catheter a demeure:				
< 24 hours	14	9	23	6.35
24-48 hours	14	20	34	9.39
24-72 hours	4	13	17	4.70
> 72 hours	23	18	41	11.33
Drain fluid production:				
missing	5	7	12	3.31
< 250 ml	11	16	27	7.46
250-500 ml	60	73	133	36.74
500-750 ml	39	39	78	21.55
> 1000 ml	60	52	111	30.94
Day drain removal:				
1-3rd day	156	169	325	89.78
4th day	14	15	29	8.01
5th day	4	1	5	1.38
> 5th day	1	2	3	0.83
Anticoagulation medication:				
coumarine	119	129	248	68.51
coumarine + heparin	35	38	73	20.17
coumarine + (reo)macrodex	8	9	17	4.70
other	13	11	24	6.63

	1 dose	3 doses	total	(%)
Situation at discharge:				
wound not healed	6	7	13	3.59
temperature elevated	3	3	6	1.66
painful/limited function	13	14	27	7.46
difficult reconvalescence	19	23	42	11.60
Preoperative sediment (> 5 leucos):				
no	120	113	233	64.36
yes	20	32	52	14.36
COMPLICATIONS:				
orthopaedic (conservative)	4	5	9	2.49
reoperation mechanical	0	4	4	1.10
general complication clean	6	2	8	2.21
general complication not clean	0	3	3	0.83
invasive diagnostics	0	1	1	0.28
clean general surgery	2	2	4	1.10
not clean surgery	0	1	1	0.28
other elective surgery	5	5	10	2.76
death in hospital	1	0	1	0.28
CULTURES knee				
Wound cultures:				
positive	10	8	18	4.97
negative	6	11	17	4.70
Operative cultures:				
positive	0	2	2	0.55
negative	32	43	75	20.72
Drain culture:				
positive	12	6	18	4.97
negative	53	62	115	31.77
Urine preoperative:				
positive	6	5	11	3.04
negative	9	13	22	6.08
Urine postoperative:				
positive	32	34	66	18.23
clinical diagnosis	0	1	1	0.28
negative	13	24	37	10.22
Pulmonary tract:				
clinical diagnosis	0	1	1	0.28
negative	3	4	7	1.93

	1 dose	3 doses	total	(%)
Skin:				
positive	1	0	1	0.28
clinical diagnosis	1	4	5	1.38
Blood:				
positive	0	2	2	0.55
negative	10	12	22	6.08
Other:				
positive	1	1	2	0.55
ADDITIONAL ANTIBIOTICS (POSTOPERATIVE) knee				
Wound	11	15	26	7.18
Urine preoperative	3	3	6	1.66
Urine postoperative	25	31	56	15.47
Pulmonary tract	0	1	1	0.28
Skin	1	1	2	0.55
Other infections	1	2	3	0.83
Temperature eci	8	7	15	4.14
Other reasons	3	2	5	1.38
FOLLOW-UP knee				
Mean follow-up (days)	392	375	-	
Mechanical reoperations	8	18	26	7.18
(Joint sepsis after reoperation	2	1	3	0.83)
Joint sepsis	3	6	9	2.49

Supplement IIa: General summary of the risk factors (univariate analysis - 2651 hip replacements)

PREOPERATIVE RISK FACTORS hip			infections		
		n	n	%	p value
Sex	male	553	3	0.54	0.74
	female	2098	14	0.67	
Age (years)	0-64	762	3	0.39	0.31
	>=64	1889	14	0.74	
Cefuroxime dose	one	1327	11	0.83	0.23
	three	1324	6	0.45	
Quetelet index	missing	436	3	0.69	0.39
(kg/m^2)	0-30	1873	10	0.53	
	> 30	342	4	1.17	
Physical condition	good	2225	14	0.63	0.85
	moderate	390	3	0.77	
	poor	36	0	0.00	
Preop. hospital stay	0	132	2	1.52	0.20
(days)	>=1	2504	15	0.60	
Preop. infections	yes	71	0	0.00	0.95
	no	2580	17	0.66	
Preop. urine sediment	yes	358	2	0.56	0.50
(>5 leucocytes/field)	no	1690	13	0.77	
	-	603	2	0.33	
Use of steroids	yes	69	-	0.00	0.50
	no	2582	17	0.66	
Diabetes	yes	100	2	2.00	0.08
	no	2551	15	0.59	

PREOPERATIVE RISK FACTORS hip		n	infections n	%	p value
Diagnosis	arthrosis	2071	12	0 58	0 52
	rheum arthr	168	1	0 60	
	fracture	334	4	1 20	
	other	78	-	0 00	
Previous surgery	-	2397	14	0 58	0 05
	prosthesis	66	1	1 52	
	fracture osteosynth	63	2	3 17	
	other (80% osteotomy)	125	0	0 00	

PERIOPERATIVE RISK FACTORS hip		n	infections n	%	p value
Approach	(antero)lateral	861	6	0 70	0 80
	posterolateral	1790	11	0 61	
Use bone cement	yes	422	1	0 24	0 26
	no	2229	16	0 72	
Breakdown of sterility	yes	157	3	1 91	0 04
(90% hole in glove)	no	2494	14	0 56	
Operation	normal	2202	14	0 64	0 83
difficulty	difficult	402	3	0 76	
	very difficult	47	0	0 00	
Operation time	missing	46	0	0 00	0 61
(minutes)	0-150	2535	16	0 63	
	> 150	70	1	1 43	
Blood loss	missing	92	0	0 00	0 81
(milliliters)	1-500	1234	7	0 57	
	501-1000	943	7	0 74	
	> 1000	382	3	0 79	
Surgeon	staff	2487	17	0 68	0 29
	resident	162	0	0 00	
Wound rinse	-	1998	12	0 60	0 84
	povidone iodine	214	2	0 93	
	ab-solution	439	3	0 68	

POSTOPERATIVE RISK FACTORS hip		n	infections n	%	p value
Haematoma	no	2126	11	0.52	0.03
	light	272	1	0.37	
	moderate	181	3	1.66	
	severe	72	2	2.78	
Minor wound problems	no	2315	15	0.65	0.80
	yes	336	2	0.59	
	erythema < 1 cm	247	2	0.80	
	dehiscence	30	-	-	
	blister	34	-	-	
	wound edge necrosis	45	-	-	
Wound drainage	no	2307	7	0.30	0.000
	serous	295	4	1.36	
	pus	20	4	20.00	
	blood	29	2	6.90	
Drainage drain wound	yes	374	5	1.34	0.07
	no	2277	12	0.53	
Wound infection	yes	56	9	16.07	0.00
	no	2595	8	0.31	
Antibiotics (wound)	yes	88	8	9.76	0.00
	no	2563	9	0.35	

OTHER POSTOPERATIVE RISK FACTORS hip		n	infections n	%	p value
Urinary tract	none	1222	5	0.41	0.23
catheter	< 24	466	4	0.86	
(hours)	24-48	433	3	0.69	
	48-72	169	0	0.00	
	>72	361	3	1.39	
Day drain removal	1-3	2516	15	0.60	0.21
(days)	> 3	135	2	1.48	
Wound healed	yes	2613	13	0.50	0.00
(at hospital discharge)	no	38	4	10.53	
Temperature normal	yes	2622	16	0.61	0.06
(at hospital discharge)	no	29	1	3.45	

OTHER POSTOPERATIVE RISK FACTORS hip		n	infections n	%	p value
Painless function (at hospital discharge)	yes	2556	15	0.59	0.07
	no	95	2	2.11	
Quick reconvalescence (at hospital discharge)	yes	2479	12	0.48	0.00
	no	172	5	2.91	
Orthop. complications	yes	94	0	0.00	0.43
	no	2540	17	0.67	
Non-orthop. complication #	yes	92	5	5.43	0.00
	no	2559	12	0.47	
Non-orthop. surgery	yes	26	0	0.00	0.68
	no	2625	17	0.65	
Wound culture	-	2524	11	0.44	0.00
	neg	50	1	2.00	
	pos	77	5	6.49	
Drain culture	-	1845	9	0.49	0.00
	neg	684	3	0.44	
	pos	122	5	4.10	
Urine preop.	-	2345	15	0.64	0.58
	neg	243	1	0.41	
	pos	63	1	1.59	
Urine postop.	-	1982	8	0.40	0.00
	neg	274	-	-	
	pos	395	9	2.28	
Skin infections	-	2594	13	0.50	0.00
	pos	57	4	7.02	
Blood culture	-	2570	13	0.51	0.00
	neg	72	3	4.71	
	pos	9	1	11.11	

(# = including five patients with skin infections of whom four had joint sepsis,therefore not considered significant in risk analysis, see also skin infection)

Supplement IIb: General summary of the risk factors (univariate analysis - 362 knee replacements)

PREOPERATIVE RISK FACTORS knee		n	infections n	%	p value
Sex	male	46	2	4 35	0 39
	female	316	7	2 22	
Age (years)	0-64	75	0	0 00	0.12
	>=64	287	19	3 14	
Cefuroxime dose	one	175	3	1 71	0 36
	three	187	6	3 21	
Quetelet index	missing	55	2	3 64	0 83
(kg/m^2)	0-30	221	5	2 26	
	> 30	86	2	2.33	
Physical condition	good	287	5	1 77	0 19
	moderate	75	4	5 40	
	poor	1	-	-	
Preop hospital stay	0/1	239	5	2 16	0 50
(days)	>=2	123	4	3 25	
Preop infections	yes	6	0	0 00	0 98
	no	356	9	2.35	
Preop urine sediment	-	77	0	0 00	0 12
(>5 leucocytes/field)	yes	49	3	5 77	
	no	227	6	2.58	
Use of steroids	yes	34	1	2 94	0 86
	no	328	8	2 44	
Diabetes	yes	17	1	5 88	0 36
	no	345	8	2.32	
Diagnosis	arthrosis	248	3	1 29	0 05
	rheum arthr.	107	6	5 94	
	other	7	0	0.00	

PREOPERATIVE RISK FACTORS knee			infections		
		n	n	%	p value
Previous surgery	-	282	6	2.13	0.21
	prosthesis	7	1	14.29	
	osteotomy	24	1	4.17	
	other	48	1	2.04	

PERIOPERATIVE RISK FACTORS knee			infections		
		n	n	%	p value
Use bone cement	yes	275	8	2.91	0.60
	no	87	1	1.14	
Breakdown of sterility	yes	15	0	0.00	0.53
(90% hole in glove)	no	347	9	2.59	
Operation	normal	300	6	2.00	0.31
difficulty	difficult	56	3	4.83	
	very difficult	6	0	0.00	
Operation time	missing	3	0	0.00	0.46
(minutes)	0-150	346	8	1.43	
	> 150	13	1	7.69	
Blood loss	missing	170	4	2.35	0.69
(milliliters)	1-500	169	5	2.96	
	> 500	23	0	0.00	
Surgeon	staff	335	9	2.62	0.49
	resident	18	0	0.00	

POSTOPERATIVE RISK FACTORS knee			infections		
		n	n	%	p value
Haematoma	yes	95	4	4.21	0.21
	no	267	5	1.87	
Minor woundhealing	yes	68	4	5.88	0.05
problems	no	294	5	1.70	
	erythema < 1 cm	35	1	2.86	
	pus suture	2	-	-	
	dehiscence	26	2	7.69	
	blister	3	-	-	
	skin necrosis	12	3	25.00	
Wound drainage	no	294	5	1.70	0.01
	serous	51	2	3.92	
	pus	4	1	25.00	
	blood	13	1	7.69	

POSTOPERATIVE RISK FACTORS knee		n	infections n	%	p value
Drainage vacuum-drain wound	yes	11	0	0 00	0 59
	no	351	9	2 56	
Wound infection	yes	13	3	23 08	0 00
	no	349	6	1 72	
Antibiotics (wound)	yes	26	5	19 23	0 00
	no	336	4	1 17	

OTHER POSTOPERATIVE RISK FACTORS knee		n	infections n	%	p value
Urinary tract catheter (hours)	none	219	7	3 10	0 80
	< 24	44	1	2 27	
	24-48	34	0	0 00	
	48-72	17	0	0 00	
	>72	41	1	2 44	
Day drain removal (days)	1-3	325	9	2 77	0 30
	> 3	37	0	0 00	
Wound healed (at hospital discharge)	yes	349	5	1 43	0 00
	no	13	4	30 77	
Temperature normal (at hospital discharge)	yes	356	8	2 25	0 02
	no	13	1	16 67	
Painless function (at hospital discharge)	yes	335	5	1 49	0 00
	no	27	4	14 81	
Quick reconvalescence (at hospital discharge)	yes	320	5	1 56	0 00
	no	42	4	9 52	
Orthop complications	yes	9	0	0 00	0 63
	no	353	9	2 35	
Non-orthop compl	yes	11	1	9 09	0 15
	no	351	8	2 28	
Non-orthop reop	yes	357	9	12 52	0 72
	no	5	0	0 00	
Wound culture	-	327	5	1 53	0 00
	neg	17	1	5 88	
	pos	18	3	16 67	

OTHER POSTOPERATIVE RISK FACTORS knee			infections		
		n	n	%	p value
Drain culture	-	228	5	2.18	0.60
	neg	115	4	3.48	
	pos	18	0	0.00	
Urine preoperative	-	329	7	2.13	0.11
	neg	22	2	9.09	
	pos	11	0	0.00	
Urine postoperative	-	258	6	2.33	0.95
	neg	67	2	2.99	
	pos	37	1	2.70	
Skin infections	-	356	8	2.25	0.02
	pos	6	1	16.67	
Blood culture	-	338	7	2.07	
	neg	22	2	9.52	0.22
	pos	2	0	0.00	

Supplement IIIa: Preoperative diagnosis and postoperative woundhealing of patients diagnosed with joint sepsis

preoperative data						postoperative data				
	age	sex	dose proph	diagn	type repl	cement	haema-toma	minor w p	drain-age	wound inf
no	a	b	c	d	e	f	g	h	i	j
1	63	f	1	fos	th	a-/f-	-	eryt	-	-
2	65	f	3	o	th	a+/f+	+++	-	ser	inf
3	75	m	1	o	th	a+/f+	++	-	bl	inf
4	73	f	3	o	th	a+/f+	-	-	-	-
5	75	f	1	f	th	a+/f+	-	-	pus	inf
6	72	m	3	fos	th	a+/f+	-	-	-	-
7	71	m	1	o	th	a+/f+	-	-	ser	inf
8	74	m	1	o	th	a+/f+	++	-	pus	inf
9	80	f	1	o	th	a+/f+	-	-	ser	inf
10	74	f	3	o	th	a+/f+	+++	-	pus	inf
11	73	f	1	o	th	a+/f+	+	-	-	-
12	78	f	1	o	th	a+/f+	-	-	pus	inf
13	70	f	1	fcup	threv	a-/f+	-	-	-	-
14	55	f	1	o	th	a-/f+	-	eryt	-	-
15	93	f	1	f	hh	f+	+++	deh	bl	-
16	66	f	3	ra	th	a+/f+	-	-	ser	inf
17	75	f	3	o	th	a+/f+	-	-	-	-

a) age at index operation
b) m = male, f = female
c) 1 = one dose of perioperative cefuroxime, 3 = three doses of perioperative cefuroxime
d) fos = failed osteosynthesis, o = osteoarthrosis, fcup = failed cup arthroplasty, ra = rheumatoid arthritis, ftka = failed total knee replacement, ost = osteotomy
e) th = total hip replacement, hh = hemi hip replacement, threv = revision total hip, tk = total knee replacement, tkrev = revision total knee replacement
f) + = cement, - = cementless, a = acetabular component, f = femoral component
g) - = none, + = light, ++ = moderate, +++ = severe
h) er(yt) = erythema < 1cm, d(eh) = dehiscence, p = pus suture, b = blister, n(e) = necrosis
i) ser = serous drainage, bl = blood, pus = purulent drainage
j) inf = wound infection (erythema >1 cm)

preoperative data						postoperative data				
	age	sex	dose proph	diagn	type repl	cement	haema-toma	minor w p	drain-age	wound inf
no	a	b	c	d	e	f	g	h	i	j
18	79	m	3	o	tk	+	-	er/ne	-	-
19	85	f	3	ra	tk	+	+	-	-	-
20	74	f	3	ftka	tkrev	+	-	-	-	inf
21	18	f	3	ra	tk	+	+++	-	pus	inf
22	72	f	1	o	tk	+	++	deh	sereus	-
23	85	f	3	ra	tk	+	-	-	-	-
24	70	f	1	ra/ost	tk	+	-	p/ne	ser/bl	inf
25	71	m	1	ra	tk	-	-	-	-	-
26	73	f	3	ra	tk	+	+++	d/b/n	bl	-

a) age at index operation
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j) inf = wound infection (erythema >1 cm)

Supplement IIIB: Follow-up data of patients with joint sepsis

	pain m	months >ok n	signs inf o	months >ok p	X-ray q	ESR increased r
1.	-	-	sinus	11	n	y
2	-	-	drain	1	n	-
3.	-	-	drain	1	n	-
4	r	5	-	-	y	y
5	r/w	1	sinus	1	n	y
6	r/w	5	tend	5	n	-
7	r/w	1	sinus	1	y	y
8.	r/w	1	sinus	1	y	y
9	r/w	1	ery/fe	1	n	y
10	r/w	1	sinus	1	y	y
11	r/w	6	sinus	11	y	y
12	-	-	sinus	1	n	y
13	r/w	1	-	-	y	y
14	r/w	1	-	-	y	y
15	-	-	drain	1	n	-
16	-	-	sinus	1	n	y
17	r	6	sinus	18	y	y
18	r/w	1	drain	1	-	y
19	r/w	5	eryth	5	y	y
20	r/w	1	eryth	1	-	y
21.	-	-	sinus	3	-	-
22	r/w	2	dr/er	4	-	y
23	-	-	sinus	3	-	y
24	r/w	1	sinus	1	-	-
25	r/w	10	er/fe	10	y	y
26	r/w	1	sinus	1	-	-

m) r = in rest, w = on weight-bearing
n) months pain developed after operation
o) signs inf = signs of infection, er(yth) = erythema of the wound, tend = tenderness of the wound, dr = drainage, fe = fever,
p) number of months infection signs developed after operation
q) y = yes (X-ray suspect for infection), n = no
r) ESR = erythrocyte sedimentation rate, y = yes (increased 20 mm above peroperative value or > 35 mm first hour)

Supplement IIIc: Cultures postoperative wound, vacuum-drain, postoperative urine, blood and joint at reoperation of patients diagnosed with joint sepsis

no	WOUND POSTOP	VACUUM-DRAIN POSTOP	URINE POS I OP	BLOOD SEPSIS	JOINT
1	-	-	E coli	neg	S aureus
2	-	-	P aeruginosa streptococ D	-	S aureus
3	Pr mirabilis P aeruginosa	Pr mirabilis Ps aeruginosa	-	-	Pr mirabilis
4	-	neg	Ps aeruginosa E coli	-	S epidermidis
5	S aureus streptococ D S viridans	-	Ps aeruginosa	-	-
6	-	-	E coli Pr mirabilis	-	E coli
7	-	Gram neg rods	-	neg	S aureus
8	S aureus	S aureus streptococ D	-	-	S aureus
9	S aureus	-	-	-	S aureus*
10	-	S epidermidis	-	-	Enterobacter
11	-	-	-	-	-
12	E coli Pr mirabilis	-	E coli Pr mirabilis	S aureus	-
13	-	neg	E coli streptococ D Pr mirabilis	-	neg
14	-	neg	-	-	negative
15	-	Enterobacter	Pseudomonas	-	Enterobacter
16	S aureus	-	-	-	S aureus
17	-	-	streptococ D E coli	-	S aureus
18	neg	-	-	-	Peptococcus
19	-	neg	-	-	neg
20	-	neg	neg	neg	S epidermidis
21	Peptococcus	neg	-	-	S epidermidis
22	Bacillus Difteroid rods	-	-	-	S aureus
23	-	-	-	-	S aureus
24	Enterobacter	-	E coli	neg	Enterobacter E coli
25	-	-	-	-	S aureus
26	-	-	-	-	S aureus

(neg = negative culture, - = culture not done, * = from aspiration culture)

Supplement IIId: Treatment of patients with joint sepsis

	SURGICAL TREATMENT s	ANTIBIOTIC TREATMENT t	OUTCOME u	NUMBER OPERATIONS v	INFECTION CURED w	F-UP MONTHS x
1	D	loc + syst	p i s	2	no	16
2	D	syst	p i s	1	yes	18
3	D	syst	p i s	1	yes	19
4	Ex Acet	loc (cement)	p i s	1	no	4
5	D	loc	p i s	3	no, died	1
6	D/RP	loc + syst	res arthr	3	?, died	1
7	D/RP/Ri/RP	loc + syst	res arthr	8	no	2
8	D + RP	loc + syst	res arthr	3	?	-
9	-	chronic ab	p i s	-	no	2?
10	D	loc + syst	p i s	3	no	7
11	-	chronic ab	p i s	-	no	27
12	-	chronic ab	p i s	-	no	12
13	RP	loc + syst	res arthr	2	yes	3
14	RP	loc + syst	res arthr	2	yes	1
15	D	syst	p i s	1	yes	16
16	D	loc + syst	p i s	2	yes	17
17	D	loc + syst	p i s	2	no	1
18	D/RP	loc + syst	res arthr	8	?	1
19	RP/Ri	loc + syst	new p i s	6	yes	8
20	D/RP/Am	loc + syst	amputation	5	yes	25
21	D/RP/Ri	loc + syst	new p i s	6	yes	12
22	D/RP	loc + syst	arthrodesis	4	yes	10
23	D	syst	p i s	1	no, died	1
24	D	loc + syst	arthrodesis	5	?	1
25	D	syst	p i s	1	no, died	1
26	RP	loc + syst	arthrodesis	2	yes	9

s) D = debridement, RP = removal prosthesis, Ri = reimplantation, Am= amputation, Ex Acet = Exchange acetabulum
t) loc = local antibiotic treatment with gentamicin beads or (if stated) gentamicin cement, syst = systemic antibiotics
u) p i s = prosthesis in situ, res arthr = resection arthroplasty, new p i s = new prosthesis in situ
w) died = sepsis-related!
x) f-up =follow-up after last operation

Curriculum vitae

Ate B. Wymenga

6 Februari 1957 : Geboren te Oudega (Smallingerland)

1969 - 1975: Atheneum-B, Ubbo Emmius Lyceum, Stadskanaal

1975 - 1976: Studie Biologie, R.U. Groningen

1976 - 1977: Militaire dienst

1977 - 1981: Studie Geneeskunde, R.U. Groningen

1981 - 1984: Studie Geneeskunde, R.U. Utrecht

1984 - 1986: Arts-assistent orthopaedie, Andreas Ziekenhuis Amsterdam, dr. S.A. Cohen †, dr. I.J. Hololtcheff

1986 - 1989: Wetenschappelijk onderzoeker, Instituut voor Orthopaedie, Radboud Ziekenhuis Nijmegen, Prof. dr. T.J.J.H. Slooff

1990 - heden:Arts-assistent algemene heelkunde, vooropleiding voor Orthopaedie, Deventer Ziekenhuizen, opleider dr. P.J. Van Elk

Stellingen

behorende bij het proefschrift
'Joint sepsis after prophylaxis
with one or three doses
of cefuroxime in hip and knee
replacement'

Ate B. Wymenga

Nijmegen 3 mei 1991

I.

Wondinfectie na een heupvervangende operatie is de enige wondstoornis, waarvoor antibiotische therapie geïndiceerd is. Alle andere stoornissen in de wondgenezing behoeven geen antibiotische therapie.

II.

Hematoomvorming in combinatie met wondinfectie na een heup- of knie-arthroplastiek is een indicatie voor chirurgische evacuatie van het hematoom.

III.

Het verhoogde risico voor prothese-infectie van patiënten met een urineweginfectie na een heupvervangende operatie, kan niet verklaard worden door hematogene infectie vanuit de urinewegen.

IV.

Er is geen relatie tussen het gebruik van een blaascatheter na een heup- of knie-arthroplastiek en infectie van de endoprothese.

V.

Tijdens een gewrichtsvervangende operatie dient de lucht in de operatiekamer minder dan 10 bacterie-dragende deeltjes per kubieke meter te bevatten.
(W. Whyte et al, *J. Hosp. Inf. 4:* 133-139, 1983)

VI.

Evenals ons wagenpark dienen ook luchtverversingssystemen van operatiekamers een Algemene Periodieke Keuring te ondergaan.

VII.

Het zou de trial rapportage ten goede komen indien onderzoekers minder geobsedeerd waren door significantie testen en zich meer zouden concentreren op het schatten van de mogelijke omvang van het behandelingseffect, uitgedrukt in het 95% betrouwbaarheidsinterval.
(S.J. Pocock, *Clinical Trials, a practical approach,* 1988)

VIII.

De tijd heelt veel wonden, maar meestal niet die van endoprothese infecties.

IX.

De mededeling van sommige orthopaeden dat zij bij prothese implantaten nooit infecties zien, dient met enige s(c)epsis beoordeeld te worden.

X.

De classificatie van enkelfracturen volgens Weber is niet geschikt om te beslissen of een enkelfractuur conservatief dan wel operatief behandeld moet worden, omdat binnen de type B-fracturen letsels vallen die een verschillende behandeling behoeven.
(C.A. Cedell, *Acta Orthop. Scand. 56:* 101-102, 1985)

XI.

De bepaling van de leucocyten bij patiënten met verdenking op acute appendicitis draagt niet bij tot de diagnose als de klachten korter duren dan 12 uur of langer dan 48 uur.
(Persoonlijke mededeling A.A.P. project Comac B.M.E.)

XII.

Uit infectie-profylactisch oogpunt dienen er meer vrouwen tot orthopaedisch chirurg te worden opgeleid, omdat vrouwen beduidend minder bacterie-dragende huidschilfers strooien dan mannen.
(J. Hill et al, *Lancet:* 1131-1133, 1974)

XIII.

Een nadeel van het gebruik van een tekstverwerker met standaard operatieverslagen en ontslagbrieven is, dat er tussen de regels niets meer te lezen valt.

Nijmegen, 3 mei 1991
Ate B. Wymenga